# Summary of Safety and Effectiveness Data

# The Eclipse TMR Holmium Laser System

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## Eclipse TMR Holmium Laser System

## Eclipse Surgical Technologies, Inc.

## 1. General Information

Device Generic Name: ..... Transmyocardial Revascularization (TMR) device

Device Trade Name: ..... Eclipse TMR Holmium Laser System

Includes:
- TMR 2000 Holmium Laser
- CrystalPoint® Fiberoptic
- CrystalFlex® Fiberoptic
- SoloGrip® II Handpiece
- J-Grip® Handpiece
- SoloGrip® I Handpiece
- SoloGrip® IP Handpiece

Applicant's Name and Address: ..... Eclipse Surgical Technologies, Inc.
1049 Kiel Ct.
Sunnyvale, CA 94089

PMA Application Number: ..... P970029

Date of Panel Recommendation: ..... October 27, 1998

Date of Notice of Approval to the Applicant: ..February 11, 1999

## 2. Indications and Usage

Transmyocardial revascularization with the Eclipse TMR System is indicated for treatment of stable patients with angina (Canadian Cardiovascular Society Class 4) refractory to medical treatment and secondary to objectively demonstrated coronary artery atherosclerosis and with a region of the myocardium with reversible ischemia 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 Eclipse TMR Holmium Laser System is composed of the Eclipse TMR 2000 Holmium: YAG laser, fiberoptic delivery systems and handpieces. The laser radiation emitted from this system has a wavelength of approximately 2.1 microns, which is in the mid-infrared (invisible) range of the electromagnetic spectrum. Water is the target absorber for this laser wavelength. This laser emits 200 microsecond laser radiation pulses at a 5 Hertz pulse repetition rate. The maximum average power is 20 Watts (4 Joules/pulse), while typical clinical levels are in the 6-8 Watt range (1.2-1.6 Joules/pulse). These pulses are not synchronized with the cardiac cycle, and there is no visible aiming beam.

The laser energy is delivered to the target tissue via fiberoptics. Two fiberoptic systems have been designed for this purpose, a single solid core fiber of approximately 1 mm diameter (CrystalPoint®) and a fiber bundle (CrystalFlex®) composed of 37 fibers (100 micron diameter each) also with an overall diameter of approximately of 1 mm. There are two fiberoptics and four surgical handpieces which are used to deliver the fiberoptics to the myocardial tissue:

| | |
|---|---|
| ***Fiberoptics*** | |
| CrystalPoint® | Single-fiberoptic to deliver laser energy |
| CrystalFlex® | Multiple-fiberoptic bundle to deliver laser energy |
| ***Handpieces*** | |
| SoloGrip® II | Single-handed disposable handpiece with integrated CrystalFlex® fiberoptic |
| SoloGrip® I | Single-handed reusable handpiece to deliver CrystalFlex® fiberoptic |
| SoloGrip® IP | Single-handed reusable handpiece with Grip-tip® to deliver CrystalFlex® fiberoptic |
| J-Grip® | Reusable handpiece to deliver CrystalFlex® fiberoptic |

## 6. Alternative Practices or 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. A laser system is commercially available in the United States.

## 7. Marketing History

The Eclipse TMR Holmium Laser System has been marketed in the following countries: Germany, Italy, Belgium, The Netherlands, Luxembourg, Denmark, the United Kingdom, Ireland, Greece, Spain, Portugal, Austria, Finland, and Sweden. No device has been withdrawn from any country or site for any reason relating to safety or effectiveness.

# 8. Adverse Events

## 8.1 Observed Adverse Events

The randomized trial of TMR using the Eclipse TMR System versus medical management (MM) involved 275 patients who were followed for a total of 204 patient-years.

There was one intra-operative death in the TMR group, which occurred in a patient who did not receive TMR – the patient developed ventricular fibrillation which could not be converted during preparation of the heart for TMR. Within 30 days of TMR, five other patients died of cardiac causes and one died of pulmonary causes. In the MM group, two patients died within 30 days of enrollment in the study, both due to cardiac causes. During 12 month follow-up, an additional nine patients in the TMR arm died (six due to cardiac causes, one each due to renal causes, multi-system organ failure and sudden death), and an additional five patients died in the MM arm (all due to cardiac causes).



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Adverse Events were reviewed by an independent, masked Data Safety and Monitoring Board (DSMB).

**Table 8-1: Adverse Events**

All patients in the Randomized Trial (n=275)

Includes all adverse events, both related and unrelated to TMR, sorted alphabetically.

| | TMR (N=132) | | MM (N=143) | |
|---|---|---|---|---|
| **Adverse Event** | **Early (0-30 days)** | **Total (0 days to 1 yr)** | **Early (0-30 days)** | **Total (0 days to 1 yr)** |
| Any Adverse Event | 39% (51) | 55% (72) | 22% (31) | 56% (80) |
| Angina/Chest Pain Requiring Re-hospitalization | 2.3% (3) | 17% (22) | 16% (23) | 44% (63) |
| Arrhythmia, Atrial | 9.8% (13) | 11% (14) | 0.7% (1) | 0.7% (1) |
| Arrhythmia, Operative Ventricular Fibrillation (Op VF) | 8.3% (11) | N/A | N/A | N/A |
| Arrhythmia, Other ventricular arrhythmia | 12% (16) | 13% (17) | 0% (0) | 0% (0) |
| Congestive Heart Failure | 3.8% (5) | 5.3% (7) | 1.4% (2) | 4.2% (6) |
| Death (all causes) | 5.3% (7) | 13% [a] | 1.6% (2) | 8.6% [a] |
| Dyspnea | 0% (0) | 0% (0) | 1.4% (2) | 8.4% (12) |
| Hypotension | 9.8% (13) | 11% (14) | 0% (0) | 0% (0) |
| Myocardial Infarction | | | | |
| Q Wave MI | 0.8% (1) | 1.7% [a] | 0.8% (1) | 3.8% [a] |
| Non Q Wave MI | 4.5% (6) | 12% [a] | 0.8% (1) | 6.7% [a] |
| Pleural Effusion | 0% (0) | 2.3% (3) | 0% (0) | 0% (0) |
| Respiratory Insufficiency | 3.0% (4) | 3.0% (4) | 0% (0) | 0% (0) |
| Systemic Infection | 1.5% (2) | 1.5% (2) | 0% (0) | 0% (0) |
| Transfusion Required | | | | |
| Due to blood loss from TMR | 0% (0) | N/A | N/A | N/A |
| Due to other reasons | 1.5% [b] (2) | 1.5% (2) | 0% (0) | 0% (0) |
| Unstable Requiring I.V. Anti-Anginals | 1.5% (2) | 17% (22) | 19% (27) | 48% (68) |

*The following events were reported only once in patients treated with TMR: allergic reaction, grand mal seizure, hemothorax, cardiomyopathy, pericarditis, peripheral edema, pneumothorax, pulmonary embolus.*

The following events were reported only once in patients treated with MM: cardiogenic shock, dehydration, pneumonia.

[a] *Survival estimated using Kaplan-Meier methods*

[b] *1 due to GI bleed, 1 due to pre-existing anemia*

*Note: Some patients experienced more than one adverse event*

### 8.2 Potential Adverse Events

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

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

## 9. Summary of Pre-Clinical Studies

### 9.1 Biocompatibility Testing

All patient contacting components of the fiberoptic delivery systems and handpieces underwent biocompatibility testing in accordance with FDA General Program Memorandum #G95-1, which provides an FDA-modified matrix of International Standard ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing." The patient contacting components of the SoloGrip® I, SoloGrip® IP, and J-Grip® handpieces are composed of stainless steel with known biocompatibility. CrystalPoint®, CrystalFlex® and SoloGrip® II successfully passed cytotoxicity, sensitization, intracutaneous toxicity, acute systemic toxicity, and hemolysis testing.

### 9.2 Sterility Testing

The CrystalPoint®, CrystalFlex®, and SoloGrip® II are single-use devices which are provided pre-sterilized to the user. These devices are sterilized using an ethylene oxide (EtO) cycle. The SoloGrip® I, SoloGrip® IP and J-Grip® reusable handpieces are sterilized by the user, with a recommended steam autoclave cycle. All of the sterilization cycles were validated to assure that the cycles successfully sterilize the devices to a Sterility Assurance Level (SAL) of $10^{-6}$. Table 9-1 summarizes the sterilization validations performed.

**Table 9-1: Summary of Sterility Testing**

| Device | Validation Test Method | Test Results |
|---|---|---|
| **CrystalPoint®** | Testing was performed using the overkill method. The following residual levels were measured: ethylene oxide (EtO), ethylene chlorohydrin (ECH) and ethylene glycol (EG). | All fibers tested met the SAL acceptance criteria. All fiber residual levels met the acceptance criteria. Testing demonstrated that the fiber can be successfully sterilized using the specified EtO cycle. |
| **CrystalFlex®** | The CrystalFlex® fiber is incorporated in its entirety into the SoloGrip® II handpiece. Therefore, the sterilization validation performed on the SoloGrip® II also served as the validation for the CrystalFlex®. | |
| **SoloGrip® II** | Testing was performed using the overkill method. The following residual levels were measured: EtO, ECH, and EG. | All devices tested met the SAL acceptance criteria. All device residual levels met the acceptance criteria. Testing demonstrated that the device can be successfully sterilized using the specified EtO cycle. |
| **SoloGrip® I and SoloGrip® IP** | Testing was performed using the overkill method. | Testing demonstrated that the SAL acceptance criteria will be achieved with the recommended steam autoclave sterilization cycle. |
| **J-Grip®** | Testing was performed using the overkill method. | Testing demonstrated that the SAL acceptance criteria will be achieved with the recommended steam autoclave sterilization cycle. |

***Shelf Life Studies***

Thirteen month accelerated aging studies were performed on the CrystalPoint® and CrystalFlex® devices. These studies demonstrated that the sterility, package integrity, and product functionality is maintained for a minimum of 13 months. Based on these results, a shelf life of one year has been established for these devices. The SoloGrip® II has a shelf life of 1 year.

## 9.3 *Device Functionality Testing*

Table 9-2 summarizes the function, strength and durability testing.

**Table 9-2: Summary of *In Vitro* Testing**

| Device | Test Description | Test Results |
|---|---|---|
| **CrystalPoint®** | Tissue Ablation in bovine heart tissue. Testing was performed to demonstrate that the fiber can effectively create 1 mm channels when used with the laser operating at 5 Hz and 6-8 watts. | The fiber was able to create 1 mm channels at the specified operating parameters. |
| | Optical Fiber Damage Test. 4 Joules/pulse of laser energy were delivered through the fiber. Fiber distal and proximal ends were visually inspected with a microscope for damage. | No fiber failures were observed. Testing demonstrated that the fiber can withstand a minimum of 500 pulses with no visual damage to the tips. |
| **CrystalFlex®** | Tissue Ablation in bovine heart tissue. Testing was performed to demonstrate that the fiber can effectively create 1 mm channels when used with the laser operating at 5 Hz and 3.2 joules/pulse. The tip was visually inspected with a microscope for damage. | A total of 60 1 mm channels were created with the fiber at the specified operating parameters. No damage was observed at the tip. |
| | Tensile Test to test the joint between the tip band and the distal tip subassembly. The tensile force necessary to break the joint was recorded. Tensile strength ≥1 lb. was considered acceptable. | All samples exceeded the minimum tensile strength criteria. |
| **SoloGrip® II** | Rotation Knob. Knob was rotated 360° 80 times in each direction. Device was inspected for damage at completion of testing. | Testing was successfully completed on all handpieces tested with minimal wearing on components. |
| | Finger Slide. Finger slide was advanced and retracted 100 times. Device was inspected for damage at completion of testing. | Testing was successfully completed on all handpieces with no stress or wear on components |
| | Depth Stop/Slide Mechanism. Depth stop control was pushed to the left, middle and right positions, and the fiber was advanced using the slide button at each position. Testing was repeated for 50 cycles. | Each sample performed as intended for 50 cycles without failure. |
| | Tensile Test to test the joint between the foam disk and the vacuum cup. The tensile force necessary to break the joint was recorded. Tensile strength ≥1 lb. was considered acceptable. | All samples exceeded the minimum tensile strength criteria. |

### 9.4 Electrical and Software Safety Testing

The TMR 2000 laser was tested and found to be in compliance with IEC 601-1, for general safety requirements for medical electrical equipment, and IEC 601-2-22 requirements for laser equipment. The TMR 2000 laser was also found to be in compliance with IEC 601-1-2 testing for electromagnetic compatibility.

The TMR 2000 laser system contains software. The software was validated as part of the laser system validation.

## 10. Summary of Clinical Studies

The Eclipse TMR Holmium Laser System was evaluated in a prospective, randomized, controlled trial which compared TMR with medical management (MM). A total of 275 patients were enrolled in the study between March 1996 and July 1998.

### 10.1 Study Design

This multi-center, prospective, randomized controlled trial was conducted at 18 U.S. sites. The study was conducted in patients with Canadian Cardiovascular Society Class 4 angina, ejection fraction >25%, and an area of reversible ischemia, who were not candidates for other interventions. Patients were excluded from the study if they had a Q wave MI within the previous 3 weeks or a non-Q wave MI within the previous 2 weeks, if they were severely unstable (i.e. unweanable from I.V. anti-anginal medication), if they had uncontrolled ventricular tachy-arrhythmia, or if they had decompensated cardiac failure.

In the original study plan, 160 patients were enrolled between March 1996 and February 1997; 74 to TMR and 86 to MM. All 160 patients reached the one year follow-up time point. Between February 1997 and July 30, 1998, an additional 115 patients (58 TMR, 57 MM) were enrolled in the study which remained open while the PMA application was under FDA review. Thus, a total of 275 patients were enrolled in the study through July 30, 1998; 132 were randomized to TMR and 143 were randomized to MM. Prior to 12 months follow-up, 46 patients in the MM group met *a priori* defined treatment failure criteria, became unstable, were withdrawn from this study, and rolled over (RO) to a separate study of TMR in unstable patients, leaving 97 patients in the MM group.

The objectives of the study were to evaluate whether the Eclipse TMR holmium laser system, when used to create small holes through the myocardium, could provide improvement at 12 months in the following endpoints: angina improvement, thallium scan parameters, all cause mortality, myocardial infarction, event free survival, treatment failure, rehospitalization for cardiac causes, and medication use. Additional endpoints analyzed included masked angina validation, quality of life, and exercise treadmill tests.

### 10.2 Patient Description and Gender Bias

Patients were randomized into the study between March 1996 and July 1998 at 18 United States centers. Patients were randomly assigned to the two treatment groups: 132 to transmyocardial revascularization (TMR) and 143 to medical management (MM). The patient baseline characteristics and cardiac risk factors are described in Table 10-1.

**Table 10-1: Patient Baseline Characteristics and Cardiac Risk Factors**

| | TMR | MM | Difference (TMR-MM) [CI] |
|---|---|---|---|
| n patients = | 132 | 143 | |
| Male | 74% (98) | 76% (108) | -2% [-12%, 9%] |
| Age (Years) | | | |
| Mean ± SD | 60 ± 10 | 60 ± 11 | 0 [-0.2, 0.2] |
| Range {Min, Max} | {32, 83} | {35, 82} | |
| Pre Ejection Fraction (%) | | | |
| Mean ± SD | 47 ± 11 | 47 ± 10 | 0 [-0.2, 0.2] |
| Range {Min, Max} | {25, 77} | {25, 70} | |
| History of Diabetes | 46% (60/131) | 48% (68) | -2% [-14%, 10%] |
| History of Smoking (Ever) | 72% (95) | 72% (101/141) | 0% [-10%, 11%] |
| History of Hypertension | 70% (92) | 71% (98/138) | -1% [-12%, 10%] |
| History of Hypercholesterolemia | 79% (100/126) | 84% (110/131) | -5% [-14%, 5%] |
| Family History of CAD Before Age 55 | | | |
| Yes | 50% (66) | 45% (64) | 5% [-7%, 17%] |
| No | 29% (38) | 22% (32) | 7% [-4%, 17%] |
| Unknown | 21% (28) | 33% (47) | -12% [-22%, -1%] |
| History of MI | 64% (85) | 64% (91/142) | 0% [-11%, 12%] |
| Documented Q-wave MI | 16% (21) | 16% (23/142) | 0% [-9%, 8%] |
| History of CHF | 17% (22/129) | 26% (34/132) | -9% [-19%, 1%] |
| Previous Percutaneous Intervention (e.g. PTCA) | 48% (63) | 48% (68) | 0% [-12%, 12%] |
| Previous CABG | 86% (113) | 86% (123) | 0% [-9%, 8%] |
| History of Either Percutaneous Intervention or CABG | 92% (121) | 87% (125) | 5% [-3%, 12%] |

*There were no statistically significant differences (p>0.05) between these groups. P values calculated using Fisher's exact test, two sided, chi-square and Student's t-test.*
*CI=95% confidence interval by normal approximation*
*NOTE: Unless otherwise specified, the denominator was the total n for each specified group.*

Study inclusion and exclusion criteria were designed, and the study was carried out, to avoid gender bias in patient enrollment. Of the 275 patients enrolled, 69 (25%) were female. This proportion of female patients is consistent with the gender incidence of patients presenting for coronary artery bypass graft surgery. In a study published in JACC, 1,148 patients were female out of 5,517 patients (20%) participating in the study.[1]

The results of separate analyses of major safety and effectiveness outcomes were similar for males and females, hence, the results presented in the following analyses are representative for both men and women

## *10.3 Results*

**Results:** Table 10-2 lists the principal safety and effectiveness results. There was statistically significant difference in angina improvement, and 12 month survival (event-free, freedom from

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

treatment failure and freedom from cardiac rehospitalization). There were no apparent differences in perfusion as measured by thallium scans.

**Table 10-2: Principal Safety and Effectiveness Results**

| | TMR (n=132) | MM (n=143) | Difference (TMR-MM) [CI] |
|---|---|---|---|
| **Angina Improvement at 12 mo.** | 76% (58/76) | 32% (16/50) | 44%* [28%, 60%] |
| **Thallium Scan Results at 12 mo. (n=61)** | | | |
| Mean ± SD Δ Extent Ischemia (%) | -0.9 ± 9.4 | -0.6 ± 10.8 | -0.3 [-5.0, 5.6] |
| Mean ± SD Δ Extent Rest Defects (%) | 1.6 ± 12.5 | 2.2 ± 11.8 | -0.6 [-5.9, 7.1] |
| **Freedom from All Cause Mortality** | | | |
| 30 Day Survival | 95% | 98% | 3.7% [-1%, 8%] |
| Survival at 12 mo. (KM) | 87% | 91% | 4.9% [-2.5%, 12.3%] |
| **Event Free Survival at 12 mo. (KM)** | 55% | 31% | 24%* [12%, 35%] |
| **Freedom from Treatment Failure at 12 mo. (KM)** | 74% | 48% | 26%* [16%, 38%] |
| **Freedom From Hospitalization for Cardiac Causes at 12 mo. (KM)** | 61% | 33% | 28%* [17%, 39%] |
| **Medication Use at 12 mo.** | | | |
| Decrease in Calcium Channel Blockers (% Pts) | 56% | 24% | 32%* [14%, 50%] |
| Decrease in Beta Blockers (% Pts) | 39% | 17% | 22%* [6%, 39%] |
| Decrease in Nitrates (% Pts) | 39% | 24% | 15% [-2%, 31%] |
| **Quality of Life (DASI Score) at 12 mo.** | 21 ± 14 | 12 ± 11 | 9* [3.1, 14.9] |
| **Exercise Treadmill Tests at 12 mo.** | | | |
| Total Exercise Time (min.) | 7.9 ± 4.5 | 6.2 ± 5.6 | 1.7 [-0.6, 4.0] |
| Total Workload (METS) | 5.0 ± 0.7 | 3.9 ± 0.8 | 1.1* [0.0, 2.1] |

**=p<0.05 P value calculated using Fisher's exact test, 2-sided for proportions, Student's t-test, two sided for continuous variables, or log rank test for KM survival estimates.*

*KM: Kaplan Meier survival estimates*

*CI=95% confidence interval by normal approximation*

*Angina Improvement: Improvement in angina symptoms from baseline to 12 months by ≥2 Canadian Cardiovascular Society classes in patients who were available at 12 month follow-up.*

*Thallium Scans: A negative value indicates an improvement in a parameter. A positive value indicates a worsening.*

*Event Free Survival: Freedom from death, Q-wave MI, hospitalization for cardiac causes, CABG or percutaneous intervention.*

*Treatment Failure: Death, Q-wave MI, 2 cardiac hospitalizations within 3 months, 3 cardiac hospitalizations within 1 year, or unweanable from IV anti-anginal medications for at least 48 hours after at least 2 attempts at weaning.*

*DASI: Duke Activity Status Index for quality of life. A higher score indicates a better quality of life*

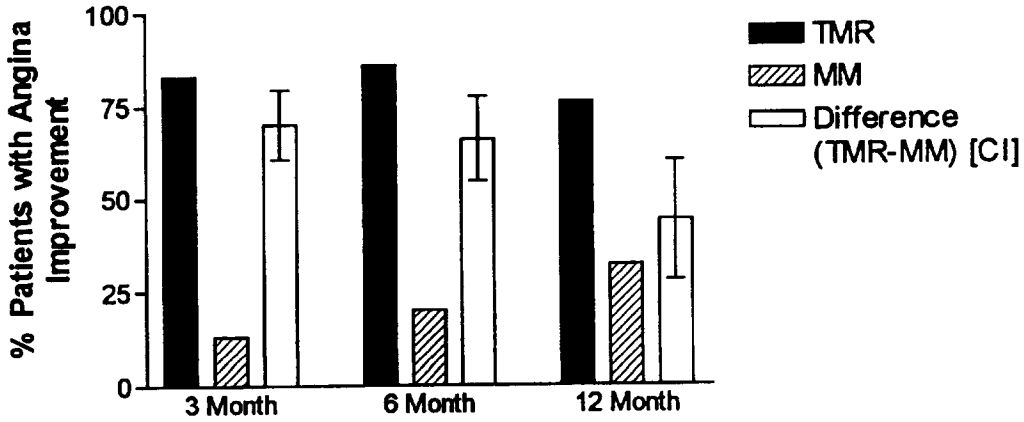
Kaplan-Meier survival estimates at 12 months were similar between the 2 groups: 87% for TMR treated patients and 91% for MM patients.

**Operative Data:** The number of TMR channels created during the procedure ranged from 16 – 87 (mean 39), using an energy range of 1.2 – 1.6 Joules per pulse (mean 1.4 J) and a mean of 13.6 pulses/channel.

**Angina Improvement:** Angina improvement was defined as improvement in angina symptoms from baseline by at least 2 angina classes, as judged by the Canadian Cardiovascular Society definition of angina. All patients had Class 4 angina at baseline. Figure 10-1 shows the percent of patients who had angina improvement at 3, 6 and 12 months follow-up. At each follow-up time point, a significantly larger number of TMR patients experienced angina improvement than MM patients, as shown by the 95% confidence intervals which exclude the 0 value. It should be noted that while the graph seems to show that more MM patients are experiencing angina improvement as time progresses, this result is actually

due to the fact that the sickest MM patients were leaving the study after failing treatment, and were rolling over to TMR.

**Figure 10-1: Angina Improvement at 3, 6 and 12 months**




| Angina Improvement | TMR | MM | Difference (TMR-MM) [CI] | P Value (TMR vs. MM) |
|---|---|---|---|---|
| 3 months | 83% (95/115) | 13% (13/98) | 70% [60%, 79%] | <0.0001 |
| 6 months | 86% (84/98) | 20% (15/74) | 66% [54%, 77%] | <0.0001 |
| 12 months | 76% (58/76) | 32% (16/50) | 44% [28%, 60%] | <0.0001 |

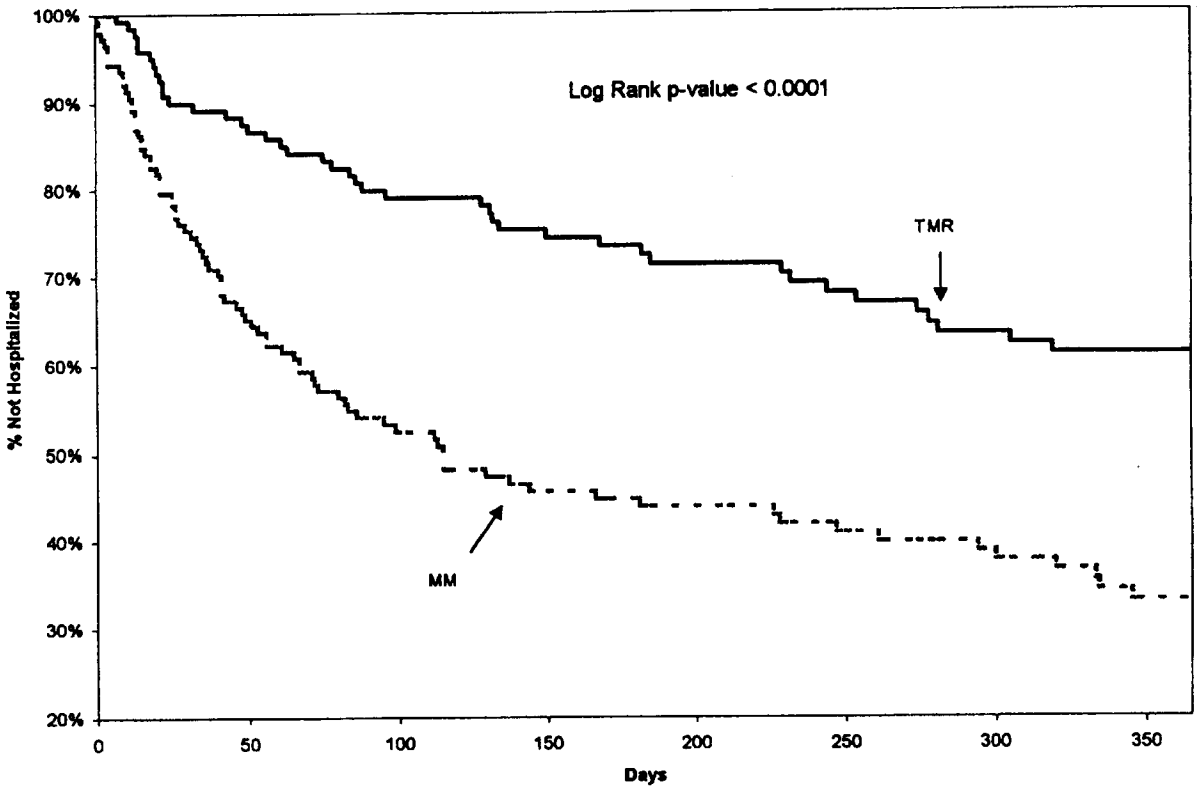
*P value calculated using Fisher's exact test, two-sided. CI=95% confidence interval by normal approximation*

An independent, masked validation of the angina assessment was conducted at an average of 3 months following the 12 month angina assessment. In 80% of the patients, the independent validation was within one class of the original angina assessment performed by the investigators. Evaluations were also similar between the two groups.

**Rehospitalizations for Cardiac Causes:** During the 12 month follow-up period, the incidence of hospital admissions for cardiac causes was statistically significantly lower in the TMR patients (32%) than the MM patients (59%). Figure 10-2 illustrates this difference using the Kaplan-Meier curve. In addition, the percent of patients who were admitted to the hospital and who required intravenous anti-anginal medications was significantly lower in the TMR group (17%) than in the MM group (48%) ($p<0.001$).

## Figure 10-2: Freedom from Cardiac Hospitalizations through 12 Months

All patients Enrolled (132 TMR + 143 MM = 275) Kaplan-Meier survival estimates




| Interval Ending (days) | 0 | 30 | 60 | 90 | 120 | 180 | 270 | 330 | 365 | Total |
|---|---|---|---|---|---|---|---|---|---|---|
| **TMR** | | | | | | | | | | |
| # Entered | 132 | 130 | 107 | 101 | 93 | 86 | 73 | 59 | 50 | 132 |
| # Censored | 0 | 6 | 1 | 1 | 4 | 6 | 8 | 4 | 0 | 30 |
| # Deaths w/o Hosps | 2 | 5 | 0 | 0 | 2 | 1 | 0 | 0 | 1 | 11 |
| # Survived w/o hosps | 130 | 107 | 101 | 93 | 86 | 73 | 59 | 50 | 49 | 49 |
| # Hospitalized | 0 | 12 | 5 | 7 | 1 | 6 | 6 | 5 | 0 | 42 |
| % Not Hospitalized | 100% | 90% | 86% | 80% | 79% | 73% | 67% | 61% | 61% | 61% |
| **MM** | | | | | | | | | | |
| # Entered | 143 | 142 | 103 | 85 | 70 | 57 | 51 | 38 | 32 | 143 |
| # Censored | 0 | 4 | 0 | 4 | 6 | 2 | 7 | 3 | 0 | 26 |
| # Deaths w/o Hosps | 0 | 2 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 3 |
| # Survived w/o hosps | 142 | 103 | 85 | 70 | 57 | 51 | 38 | 32 | 29 | 29 |
| # Hospitalized | 1 | 33 | 18 | 11 | 7 | 4 | 5 | 3 | 3 | 85 |
| % Not Hospitalized | 99% | 75% | 62% | 54% | 48% | 45% | 40% | 37% | 33% | 33% |

*Difference between TMR and MM was tested at day 365 using log rank test.*

*Interval ending describes events from the time of the previous interval up to the day the specified interval ends (i.e. the 30 day interval includes events from day 1 – day 30).*

*Interval 0 includes events occurring from enrollment to midnight on the day of enrollment.*

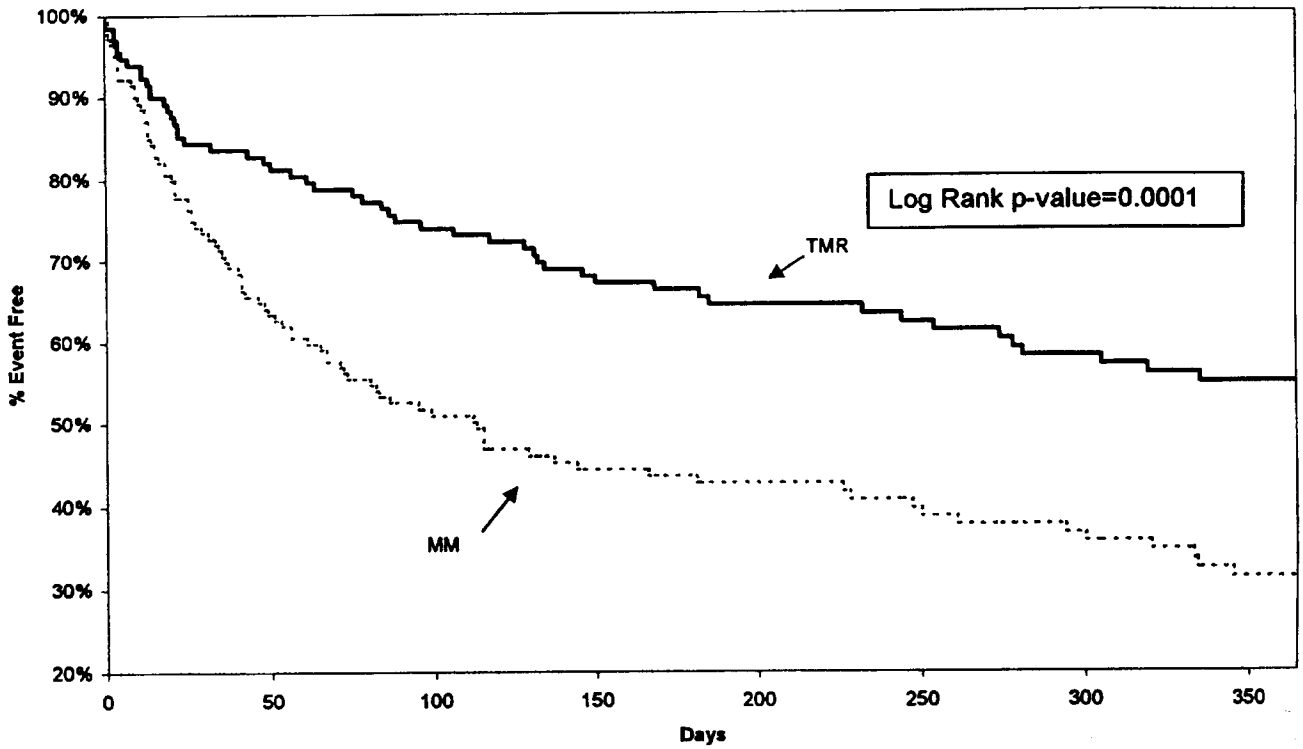
*Censored refers to a patient not available for follow-up at the designated interval (e.g. patient not at 12 months yet, lost to follow-up, etc.).*

*Deaths without Hospitalization were censored at the time of death.*

**Event Free Survival:** Event free survival was defined in this study as freedom from the occurrence of death (due to any cause), Q wave MI, hospitalization for cardiac causes, CABG or percutaneous intervention. Event free survival was compared between the two groups using Kaplan-Meier survival estimates, corrected for patients who were unavailable for follow-up. A significantly higher percentage of TMR patients (55%) were event free at 12 months, compared with MM patients (31%) ($p=0.0001$). Figure 10-3 illustrates this difference using the Kaplan-Meier curve.

## Figure 10-3: Event Free Survival through 12 Months

All patients Enrolled (132 TMR + 143 MM = 275) Kaplan-Meier survival estimates




| Interval Ending (days) | 0 | 30 | 60 | 90 | 120 | 180 | 270 | 330 | 365 | Total |
|---|---|---|---|---|---|---|---|---|---|---|
| **TMR** | | | | | | | | | | |
| # Entered | 132 | 130 | 106 | 100 | 92 | 85 | 72 | 59 | 50 | 132 |
| # Censored | 0 | 6 | 1 | 1 | 4 | 6 | 8 | 4 | 0 | 30 |
| # Event Free | 130 | 106 | 100 | 92 | 85 | 72 | 59 | 50 | 49 | 49 |
| # with Event | 2 | 18 | 5 | 7 | 3 | 7 | 5 | 5 | 1 | 53 |
| % Event Free | 99% | 84% | 80% | 75% | 72% | 66% | 61% | 56% | 55% | 55% |
| **MM** | | | | | | | | | | |
| # Entered | 143 | 142 | 102 | 84 | 69 | 57 | 51 | 38 | 32 | 143 |
| # Censored | 0 | 4 | 0 | 4 | 5 | 2 | 7 | 3 | 0 | 25 |
| # Event Free | 142 | 102 | 84 | 69 | 57 | 51 | 38 | 32 | 29 | 29 |
| # with Event | 1 | 36 | 18 | 11 | 7 | 4 | 6 | 3 | 3 | 89 |
| % Event Free | 99% | 73% | 61% | 53% | 47% | 44% | 38% | 35% | 31% | 31% |

*Event: Death, Q-wave MI, hospitalization for cardiac causes, CABG or percutaneous intervention.*

*Difference between TMR and MM was tested at day 365 using log rank test.*

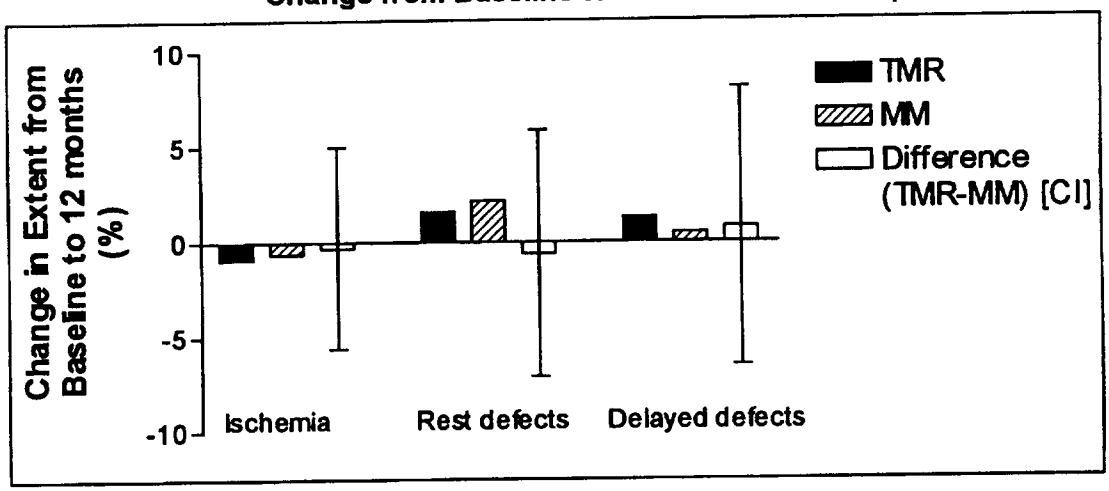
*Interval ending describes events from the time of the previous interval up to the day the specified interval ends (i.e. the 30 day interval includes events from day 1 – day 30).*

*Interval 0 includes events occurring from enrollment to midnight on the day of enrollment.*

*Censored refers to a patient not available for follow-up at the designated interval (e.g. patient not at 12 months yet, lost to follow-up, etc.).*

**Thallium Scans:** Figure 10-4 illustrates the change in the extent of ischemia, rest defects and delayed defects from baseline to 12 months follow-up. A change <10% is not considered clinically significant. All thallium scans were read by a masked core lab using computer quantification. Improvement from baseline to 12 months is indicated as a decrease in the mean score (or negative value). There were no statistically significant differences in changes in thallium scans between the two groups.

**Figure 10-4: Thallium Scan Results at 12 Months**
**Change from Baseline to 12 Months Follow-up**




| Mean (± SD) Change in Extent (%) of Variable from Baseline to 12 Months | Total | TMR | MM | Difference (TMR-MM) [CI] | P value |
|---|---|---|---|---|---|
| Ischemic | | -0.9 ± 9.4 | -0.6 ± 10.8 | -0.3 [-5.0, 5.6] | NS |
| Rest Defects | | 1.6 ± 12.5 | 2.2 ± 11.8 | -0.6 [-5.9, 7.1] | NS |
| Delayed Defects | | 1.3 ± 11.5 | 0.5 ± 12.0 | 0.8 [-6.5, 8.1] | NS |

*P value calculated using Student's t-test, two-sided. NS = not significant (p>0.05)*
*CI=95% confidence interval by Student's t-distribution.*

**Medication Use:** At 12 months follow-up, more TMR patients (56%) had decreased their use of calcium channel blockers than MM patients (24%). This difference was statistically significant (p=0.002). Increases in calcium channel blocker use was similar between the two groups with 19% of TMR patients increasing their calcium channel blocker use, compared with 26% of MM patients (p=NS).

Beta blocker use at 12 months was also decreased in a larger percentage of TMR patients (39%) than MM patients (17%) (p=0.02). The percentage of patients who increased beta blocker use was similar between the two groups (30% TMR; 29% MM; p=NS).

Nitrate use at 12 months was similar between the two groups. A decrease in nitrate use was seen in 39% of TMR patients, compared with 24% of MM patients. An increase in nitrate use was seen in 29% of TMR patients compared with 47% of MM patients.

**Quality of Life:** Quality of life was assessed at 12 months using the Duke Activity Status Index (DASI) questionnaire. The DASI questionnaire consists of 12 questions about activities that represent major aspects of physical function, including personal care, ambulation, household tasks, sexual function and recreational activities. Each answer has a weight associated with it and patients' weighted answers were summed to generate the DASI score. The highest possible score is 58.2. At 12 months, TMR patients had a mean DASI score of 21, which was statistically significantly better than the MM patients, who had a mean score of 12 (p=0.003).

**Exercise Treadmill Testing:** At 12 months follow-up, TMR patients were able to perform a statistically significantly greater workload (as measured in METS) than MM patients. TMR patients were able to perform an average of 5.0 METS, compared with 3.9 METS for MM patients (p=0.05). TMR patients were able to exercise an average of 7.9 minutes compared with 6.2 minutes for MM patients (p=NS).

**Morbidity and Mortality:** There was 1 intra-operative death in the TMR group, which occurred in a patient who did not receive TMR. Within 30 days of TMR, 5 other patients died of cardiac causes and one died of pulmonary causes. In the MM group, 2 patients died within 30 days of enrollment in the study, both due to cardiac causes. During 12 month follow-up, an additional 9 patients in the TMR arm died (6 due to cardiac causes, 1 each due to renal causes, multi-system organ failure and sudden death), and an additional 5 patients died in the MM arm (all due to cardiac causes). Kaplan-Meier survival estimates at 12 months were similar between the 2 groups: 87% for TMR treated patients and 91% for MM patients.

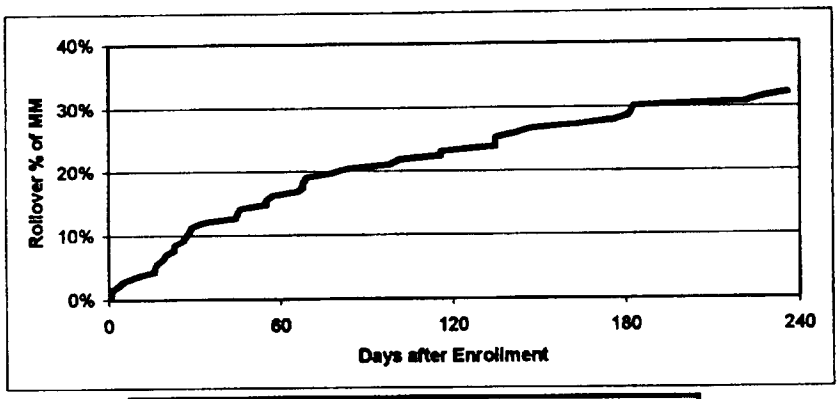
In the TMR group, 5 of 23 patients treated prior to July, 1996 died within 30 days of the procedure. Investigators attributed this result to "fluid loading" patients prior to the TMR procedure. This practice of "fluid loading" was discontinued in June, 1996. From July, 1996 to completion of enrollment in July, 1998, an additional 109 patients received TMR in the study. In this group 30 day mortality was 1.8% (2/109).

**Treatment Failure:** Treatment failure was defined in this study as the occurrence of at least one of the following events: death, Q-wave MI, 2 cardiac hospitalizations within 3 months, 3 cardiac hospitalizations within 1 year, or unweanable from IV anti-anginal medications for at least 48 hours after at least 2 attempts at weaning. Using Kaplan-Meier survival estimates, a significantly higher percentage of TMR patients (74%) had not experienced treatment failure at 12 months, compared with MM patients (48%) (p<0.0001).

**MM Patients Who Rolled Over to TMR:** Of the 143 patients randomized to MM, 46 patients met treatment failure criteria, became unstable and withdrew from the randomized study. These 46 patients then enrolled in a separate study for unstable patients and received TMR. These patients were referred to as rollover patients. The mean time to rollover was 81 days (Figure 10-5).

Peri-operative mortality (within 30 days of the TMR procedure) occurred in 4 (8.7%) rollover patients. There were no additional deaths during the 12 month follow-up period in the rollover group. At 12 months follow-up, 78% (29/37) of the rollover patients experienced angina improvement.

**Figure 10-5: Percent of Rollover of MM Patients by Day**




| | |
|---|---|
| Number Enrolled | 143 |
| Number rolled over | 46 |
| Mean days to RO | 81.0 |
| Median days to RO | 61.5 |

## 11. Conclusions Drawn from the Studies

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

Data from the multicenter clinical trial show treatment with the Eclipse TMR Holmium Laser System provides a reduction in the severity of angina in the majority of patients, but the risks of the procedure (including major cardiac arrhythmias and early death within 30 days of the operation) were increased. After one year had elapsed, the overall mortality was similar between the treated and control groups. Experience beyond one year is not yet available.

## 12. Panel Recommendation

At an advisory meeting held on October 27, 1998, the Circulatory System Devices Panel recommended that the Eclipse TMR Holmium Laser System be approved subject to submission to, and approval by, the Center for Devices and Radiological Health (CDRH) of the following:

(1) Changes to INDICATIONS FOR USAGE, WARNINGS AND PRECAUTIONS, and PATIENT COUNSELLING INFORMATION sections of the Information for Use (labeling); and a

(2) 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.

## 13. FDA Decision

FDA concurred with the Circulatory System Devices Panel's recommendation of October 27, 1998. The applicant amended the PMA to address the issues outlined above as recommended by the Panel and required by the FDA.

A randomized post approval study will be conducted to further define the 30-day post-operative mortality predictors (risk factors), effectiveness as a function of operator experience (the learning curve), and the disease characteristics of the population 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 in the form of a PMA supplement for review and approval within 30 days of the date of the approval order. Prior to initiation of the post approval study, treatment of patients will be limited to 90 days after the date of this letter and total of 90 patients. Once the post approval study is initiated, the restrictions on the number of patients will be removed.

Also as a condition of approval, the patient must sign a consent form to ensure that the risks associated with this treatment have been fully explained to the patient.

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 labeling.

**Post-approval Requirements and Restrictions**: See Approval Order