STUDY TITLE: INSPIRE (Adenosine Sestamibi Post-Infarction Evaluation)

PUBLICATION TITLE: A Multinational Study to Establish the Value of Early Adenosine Technetium-99m Sestamibi Myocardial Perfusion Imaging in Identifying a Low-Risk Group for Early Hospital Discharge after Acute Myocardial Infarction

JOURNAL: Journal of the American College of Cardiology 2006:48:12; 2448-57

AUTHOR: Mahmarian J, Shaw LJ, et al.

CONTEXT: Controversy exists as to the role of noninvasive stress imaging in stratifying risk early after acute myocardial infarction (AMI).

OBJECTIVE: To determine whether gated adenosine Tc-99m sestamibi single photon emission computed tomography (ADSPECT) could accurately define risk and thereby guide therapeutic decision making in stable survivors of acute myocardial infarction (AMI).

DESIGN, SETTING AND PATIENTS: The INSPIRE (Adenosine Sestamibi Post-Infarction Evaluation) trial was a prospective multicenter trial which enrolled 728 clinically stable survivors of AMI who had gated ADSPECT within 10 days of hospital admission and subsequent 1-year follow-up. Event rates were assessed within prospectively define INSPIRE risk groups based on the adenosine-induced left ventricular perfusion defect size, extent of ischemia, and ejection fraction.

MAIN OUTCOME MEASURES: Cardiac event and cardiac death/reinfarction, assessment of patient risk based on total and ischemic perfusion defunct size (PDS) and subsequent patient therapeutic decision-making.

CARDIOLITE® UTILIZATION: Cardiolite® was the myocardial perfusion imaging agent selected for use in the INSPIRE study. 728 clinically stable survivors of AMI had a gated adenosine Cardiolite® myocardial perfusion imaging study within 10 days of hospitalization to stratify risk early after surviving an acute myocardial infarction.

RESULTS: Total cardiac events/death and reinfarction significantly increased within each INSPIRE risk group from low (5.4%, 1.8%), to intermediate (14%, 9.2%), to high (18.6%, 11.6%) (p<0.01). Event rates at 1 year were lowest in patients with the smallest perfusion defects but progressively increased when defect size exceeded 20% (p<0.0001). The perfusion results significantly improved risk stratification beyond that provided by clinical and ejection fraction variables. The low-risk INSPIRE group, comprising one-third of all enrolled patients had a shorter hospital stay with lower associated costs compared with the higher-risk groups (p<0.001).

CONCLUSIONS: Gated ADSPECT performed early after AMI can accurately identify a sizeable low-risk group who have a <2% death and reinfarction rate at 1 year. Identifying these low-risk patients for early hospital discharge may improve utilization of health care resources at considerable cost savings.
**INDICATIONS AND USAGE FOR CARDIOLITE®:**
Indications and Usage Cardiolite®, Kit for the Preparation of Technetium Tc99m Sestamibi for Injection, is a myocardial perfusion agent that is indicated for detecting coronary artery disease by localizing myocardial ischemia (reversible defects) and infarction (non-reversible defects), in evaluating myocardial function and developing information for use in patient management decisions. Cardiolite® evaluation of myocardial ischemia can be accomplished with rest and cardiovascular stress techniques (e.g., exercise or pharmacologic stress in accordance with the pharmacologic stress agent's labeling).

It is usually not possible to determine the age of a myocardial infarction or to differentiate a recent myocardial infarction from ischemia.

**IMPORTANT SAFETY INFORMATION FOR CARDIOLITE:**
Exercise and pharmacologic stress testing should be performed only under the supervision of a qualified physician. Cardiolite® has been rarely associated with acute severe allergic events of angioedema and urticaria. The most frequently reported adverse events include headache, chest pain/angina, ST segment changes on ECG, nausea, and abnormal taste and smell.
CARDIOLITE® Kit for the Preparation of Technetium Tc99m Sestamibi for Injection

FOR DIAGNOSTIC USE

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CARDIOLITE® safely and effectively. See full prescribing information for CARDIOLITE®.

CARDIOLITE®, Kit for the Preparation of Technetium Tc99m Sestamibi for Injection. Initial U.S. Approval: December, 1990

RECENT MAJOR CHANGES
Use in specific populations (8.3)

INDICATIONS AND USAGE
CARDIOLITE® is a myocardial perfusion agent indicated for:
- detecting coronary artery disease by localizing myocardial ischemia (reversible defects) and infarction (non-reversible defects), in evaluating myocardial function and developing information for use in patient management decisions.

DOSE AND ADMINISTRATION
- For Myocardial Imaging: The suggested dose range for I.V. administration of CARDIOLITE® in a single dose to be employed in the average patient (70 Kg) is 370 - 1110 MBq (10 - 30 mCi).
- For Breast Imaging: The recommended dose range for administration of MIRALUMA® is a single dose of 740 - 1110 MBq (20 - 30 mCi).

DOSE FORMS AND STRENGTHS
- CARDIOLITE® Kit for the Preparation of Technetium Tc99m Sestamibi for Injection is supplied as a lyophilized mixture in a 5 ml vial.

CONTRAINDICATIONS
- None known

WARNINGS AND PRECAUTIONS
- Pharmacologic induction of cardiovascular stress may be associated with serious adverse events such as myocardial infarction, arrhythmia, hypotension, myocardial necrosis and cerebrovascular events.
- CARCINOMA may have been rarely associated with late effects of certain anticancer drugs and defribinoginization.
- Patients with severeystolic dysfunction may be at increased risk for the development of cardiogenic shock during cardiac catheterization.

ADVERSE REACTIONS
- The following adverse reactions have been reported in ≤ 0.5% of patients: signs and symptoms consistent with those occurring shortly after administration of the agent; transient arthritis, angina pectoris, arrhythmia, dizziness, syncope, abdominal pain, vomiting, and severe hypersensitivity characterized by dyspnea, hypotension, hypothyroid, bradycardia, asthma, and vomiting within two hours after a second injection of Technetium Tc99m Sestamibi. A few cases of flushing, edema, injection site inflammation, dry mouth, fever, pruritus, rash, urticaria and fatigue have also been attributed to administration of the agent.

Drug Interactions
- Specific drug-durg interactions have not been studied.

Use in SPECIFIC POPULATIONS
- In one study of 46 subjects who received CARDIOLITE® administration, the radioactivity in both children and adolescents exhibited blood PK profiles similar to those previously reported in adults.

Table 1.0. Radiation Absorbed Doses from Tc99m Sestamibi

<table>
<thead>
<tr>
<th>Organ</th>
<th>30 mCi</th>
<th>1110 MBq</th>
<th>30 mCi</th>
<th>1110 MBq</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breasts</td>
<td>0.2</td>
<td>0.2</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Gallbladder Wall</td>
<td>2.0</td>
<td>2.0</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Small Intestine</td>
<td>3.0</td>
<td>3.0</td>
<td>3.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Upper Large Intestine</td>
<td>5.4</td>
<td>55.5</td>
<td>5.4</td>
<td>55.5</td>
</tr>
<tr>
<td>Wall</td>
<td>3.9</td>
<td>40.0</td>
<td>4.2</td>
<td>41.1</td>
</tr>
<tr>
<td>Stomach Wall</td>
<td>0.6</td>
<td>6.1</td>
<td>0.6</td>
<td>5.8</td>
</tr>
<tr>
<td>Heart Wall</td>
<td>0.5</td>
<td>5.1</td>
<td>0.5</td>
<td>4.9</td>
</tr>
<tr>
<td>Kidneys</td>
<td>2.0</td>
<td>20.0</td>
<td>2.0</td>
<td>20.0</td>
</tr>
<tr>
<td>Liver</td>
<td>0.6</td>
<td>5.8</td>
<td>0.6</td>
<td>5.7</td>
</tr>
<tr>
<td>Lungs</td>
<td>0.3</td>
<td>3.8</td>
<td>0.3</td>
<td>3.7</td>
</tr>
<tr>
<td>Bone Surfaces</td>
<td>0.7</td>
<td>7.0</td>
<td>0.7</td>
<td>6.4</td>
</tr>
<tr>
<td>Thyroid</td>
<td>0.7</td>
<td>7.0</td>
<td>0.7</td>
<td>7.0</td>
</tr>
<tr>
<td>Ovaries</td>
<td>1.5</td>
<td>15.5</td>
<td>1.5</td>
<td>15.5</td>
</tr>
<tr>
<td>Testes</td>
<td>0.3</td>
<td>3.4</td>
<td>0.4</td>
<td>3.9</td>
</tr>
<tr>
<td>Red Marrow</td>
<td>0.5</td>
<td>5.0</td>
<td>0.5</td>
<td>5.0</td>
</tr>
<tr>
<td>Uterine Bladder Wall</td>
<td>2.0</td>
<td>20.0</td>
<td>4.2</td>
<td>41.1</td>
</tr>
<tr>
<td>Total Body</td>
<td>0.5</td>
<td>4.8</td>
<td>0.5</td>
<td>4.8</td>
</tr>
</tbody>
</table>

STRESS

Table 1.0. Radiation Absorbed Doses from Tc99m Sestamibi

<table>
<thead>
<tr>
<th>Organ</th>
<th>2.0 hour</th>
<th>4.8 hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radial</td>
<td>mCi</td>
<td>mCi</td>
</tr>
<tr>
<td>Breasts</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Gallbladder Wall</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Small Intestine</td>
<td>3.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Upper Large Intestine</td>
<td>5.4</td>
<td>55.5</td>
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<tr>
<td>Wall</td>
<td>3.9</td>
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<tr>
<td>Stomach Wall</td>
<td>0.6</td>
<td>6.1</td>
</tr>
<tr>
<td>Heart Wall</td>
<td>0.5</td>
<td>5.1</td>
</tr>
<tr>
<td>Kidneys</td>
<td>2.0</td>
<td>20.0</td>
</tr>
<tr>
<td>Liver</td>
<td>0.6</td>
<td>5.8</td>
</tr>
<tr>
<td>Lungs</td>
<td>0.3</td>
<td>3.8</td>
</tr>
<tr>
<td>Bone Surfaces</td>
<td>0.7</td>
<td>7.0</td>
</tr>
<tr>
<td>Thyroid</td>
<td>0.7</td>
<td>7.0</td>
</tr>
<tr>
<td>Ovaries</td>
<td>1.5</td>
<td>15.5</td>
</tr>
<tr>
<td>Testes</td>
<td>0.3</td>
<td>3.4</td>
</tr>
<tr>
<td>Red Marrow</td>
<td>0.5</td>
<td>5.0</td>
</tr>
<tr>
<td>Uterine Bladder Wall</td>
<td>2.0</td>
<td>20.0</td>
</tr>
<tr>
<td>Total Body</td>
<td>0.5</td>
<td>4.8</td>
</tr>
</tbody>
</table>
Breast Studies

Technetium Tc99m Sestamibi should not be used more than six hours after oxidants should not be used. Aseptic procedures during preparation. Pyrogenic. It is essential to follow directions carefully and to adhere to strict aseptic procedures during preparation. The contents of the kit before preparation are not radioactive. However, after the Sodium Pertechnetate Tc99m Injection is added, adequate shielding of the final sample to dry (typically 15 minutes). The TLC tank is prepared by pouring ethanol into the well (depth=3-4 mm) and allowing the sample spot to dry. Develop the plate in the covered TLC tank in ethanol for a distance of 5 cm from the point of application. Cut the TLC plate 4 cm from the bottom and measure the Tc99m activity in each piece by appropriate radiation detector. Calculate the % Tc99m Sestamibi as:

1. Obtain a Baker-Flex Aluminum Oxide coated, plastic TLC plate, #1 B-F, pre-cut to 2.5 x 7.5 cm.
2. Dry the plate or plates at 100°C for 1 hour and store in a desiccator. Remove pre-dried plate from the desiccator just prior to use.
3. Apply 1 drop of ethanol* using a 1 mL syringe with a 22-26 gage needle, 1.5 cm from the bottom of the plate. The SPOT SHOULD NOT BE ALLOWED TO DRY.
4. Add 2 drops of Technetium Tc99m Sestamibi solution, side by side on top of the ethanol* spot. Return the plate to a desiccator and allow the sample spot to dry (typically 15 minutes).
5. The TLC plate is then developed by pouring ethanol into the well (depth=3-4 mm). Cover the tank with a desiccator for 4 hours. Develop the plate in the covered TLC tank in ethanol for approximately 10 minutes. Develop the plate in the covered TLC tank in ethanol for a distance of 5 cm from the point of application.

ADVERSE REACTIONS

Adverse events were evaluated in 3741 adults who were evaluated in clinical studies. Of these patients, 3068 (77% men, 22% women, and 0.7% of the patient's genders were not recorded) were in cardiac clinical trials and 673 (100% women) in breast imaging trials. Cases of angina, chest pain, and death have occurred (see Section 5). Adverse events reported at a rate of 0.5% or greater after receiving Technetium Tc99m Sestamibi administration are shown in the following Table 2.0.

Table 2.0

Selected Adverse Events Reported in > 0.5% of Patients Who Received Technetium Tc99m Sestamibi in Either Breast or Cardiac Clinical Studies

Body System

Body as a Whole

Nausea

Cardiovascular

Chest Pain/Anemia

SI segment changes

Dyspnea

Hypertension

Tachycardia

Bradycardia

Vomiting

Paresthesia

Parosmia

Special Senses

Stomach

Diabetes

Hypothyroidism

Vomiting

Other

N = 685

N = 685

N = 2361

N = 3068

N = 685

N = 685

N = 685

N = 685

N = 685

N = 2361

N = 63

N = 63

N = 63

N = 63

N = 63

N = 63

N = 63

Excludes 22 patients whose gender was not recorded.

In the clinical studies for breast imaging, breast pain was reported in 12 (1.7%) of the patients. In 11 of these patients the pain appears to be associated with biopsy/surgical procedures. The following adverse reactions have been reported in < 0.5% of patients: signs and symptoms consistent with severe occurring shortly after administration of the agent, transient neutropenia, arthralgia, urticaria, hypotension, bronchospasm, and cerebrovascular events. Caution should be used when pharmacologic stress is selected as an alternative to exercise; it should be used when indicated and in accordance with the pharmacologic stress agent's labeling.

DOSAGE FORMS AND STRENGTHS

CARDIOLITE® Kit for the Preparation of Technetium Tc99m Sestamibi for Injection is supplied as a lyophilized mixture in a 5 mL vial. The contents of the vial are intended only for use in the preparation of Technetium Tc99m Sestamibi and are not to be administered directly to the patient without administering either CARDIOLITE® or Sodium Pertechnetate Tc99m Injection. Also, before administering either CARDIOLITE® or MIRALUMA®, patients should be asked about the possibility of allergic reactions to either drug.

5.2 General Precautions

The contents of the vial are intended only for use in the preparation of Technetium Tc99m Sestamibi and are not to be administered directly to the patient without first undergoing the preparative procedure. Radioactive drugs must be handled with care and appropriate safety measures should be used to minimize radiation exposure to clinical personnel. Also, care should be taken to minimize radiation exposure to the patients consistent with proper patient management. Contents of the kit before preparation are not radioactive. However, after the Sodium Pertechnetate Tc99m Injection is added, adequate shielding of the final preparation must be maintained. The components of the kit are sterile and non-pyrogenic. It is essential to follow directions carefully and to adhere to strict aseptic procedures during preparation. Technetium Tc99m labeling reactions depend on maintaining the stannous ion in the reduced state. Hence, Sodium Pertechnetate Tc99m injection containing oxidants should not be used. Technetium Tc99m Sestamibi should not be used more than six hours after preparation.

In a clinical pharmacology study, 46 pediatric patients with Kawasaki disease received CARDIOLITE® administration at the following doses: 0.1 - 0.2 mCi/kg for rest, 0.3 mCi/kg for stress in one day studies; 0.2 mCi/kg for rest and 0.2 mCi/kg for stress in two day studies. The radioactivity both in younger children and in adolescents exhibited PK profiles similar to those previously reported in adults (see Section 12). The radiation absorbed doses in adolescents, both at rest and stress, were similar to those observed in adults (see Section 2). When comparing weight-adjusted radioactivity (up to 0.3 mCi/kg) doses administered to adolescents and younger children to the recommended dose administered to adults (up to 0.3 mCi/kg), the radiation absorbed doses in both adolescents and younger children were similar to those in adults. Adverse events were evaluated in 609 pediatric patients from the three clinical studies described above. The frequency and the type of the adverse events were similar to the ones observed in the studies of CARDIOLITE® in adults. Two of the 609 had a serious adverse event: one patient received a CARDIOLITE® overdose but remained asymptomatic, and one patient had an asthma exacerbation following administration.

8.5 Geriatric Use

Of 3068 patients in clinical studies of CARDIOLITE®, Kit for the Preparation of Technetium Tc99m Sestamibi for Injection, 693 patients were 65 or older and 121 were 75 or older. Of 673 patients in clinical studies of MIRALUMA®, Kit for the Preparation of Technetium Tc99m Sestamibi for Injection, 138 patients were 65 or older and 30 were 75 or older. Based on the evaluation of the frequency of adverse events and review of vital signs data, no overall differences in safety were observed between these subjects and younger subjects. Although reported clinical experience has not identified differences in response between elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

9. DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Not applicable.

9.2 Abuse

Not applicable.

9.3 Dependence

Not applicable.

10. OVERDOSAGE

The clinical consequences of overdosing with CARDIOLITE® are not known.

11. DESCRIPTION

Each 5 mL vial contains a sterile, non-pyrogenic, lyophilized mixture of

Tetraiodo-2-methoxyisobutylisonitrile

(Copper (II) tetrafluoroborate - 1.0 mg)

Sodium Citrate Dihydrate - 2.6 mg

L-Cysteine Hydrochloride Monohydrate - 1.0 mg

Stannous Chloride, Dihydrate, minimum (SnCl2 • 2H2O) - 0.025 mg

Stannous Chloride, Dihydrate, (SnCl2 • 2H2O) - 0.075 mg

Chloride (stannous and stannic) Dihydrate, maximum (as SnCl2 • 2H2O) - 0.086 mg

Prior to lyophilization the pH is 5.3 to 5.9. The contents of the vial are lyophilized and stored under nitrogen.

This drug is administered by intravenous injection for diagnostic use after reconstitution with sterile, non-pyrogenic, oxidant-free Sodium Pertechnetate Tc99m Injection. The reconstituted product is 5.5 (± 0.4). No bacteriostatic preservative is present.

The precise structure of the technetium complex is Tc99m(MII)4−, where MII is 2-methoxyisobutylisonitrile.

12.1 Environmental Radiation

Technetium Tc99m decays by isomeric transition with a physical half-life of 6.02 hours. Photons that are useful for detection and imaging studies are listed below in Table 3.0.

Table 3.0. Principal Radiation Emission Data

<table>
<thead>
<tr>
<th>Energy (keV)</th>
<th>Decay Mode</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>140.5</td>
<td>Photopeak</td>
<td>100%</td>
</tr>
<tr>
<td>208.0</td>
<td>Isomeric</td>
<td>100%</td>
</tr>
</tbody>
</table>

To correct for physical decay of this radionuclide, the fractions that remain at selected intervals after the time of calibration are shown in Table 5.0.

Table 4.0. Radiation Attenuation Data

<table>
<thead>
<tr>
<th>Radiation</th>
<th>Mean % Disintegration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiography</td>
<td>89.0%</td>
</tr>
</tbody>
</table>

Kocher, David C., Radioactive Decay Data Tables, DOE/TC-11010, 1(1981).
12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Technetium Tc99m Sestamibi is a cationic Tc99m complex which has been found to accumulate in viable myocardial tissue in a manner analogous to that of thallous chloride Tl-201. Scintigraphic images obtained in humans after the myocardial administration of the drug have been comparable to those obtained with thallous chloride Tl-201 in normal and abnormal myocardial tissue.

Animal studies have shown that myocardial uptake is not blocked when the sodium pump mechanism is inhibited. Although studies of subcellular fractionation and electron micrograph analysis of heart cell aggregates suggest that Tc99m Sestamibi cellular retention occurs specifically within the mitochondrion as a result of electrostatic interactions, the clinical relevance of these findings has not been determined. The mechanism of Tc99m Sestamibi localization in various types of breast tissue (e.g., benign, inflammatory, malignant, fibrous) has not been established.

12.3 Pharmacokinetics

Pulmonary activity is negligible even immediately after injection. Blood clearance studies indicate the rapid and complete component with a t1/2 of 4.3 minutes at rest, and clears with a t1/2 of 1.6 minutes under exercise conditions. At five minutes post injection about 8% of the injected dose remains in circulation. There is less than 1% protein binding of Technetium Tc99m Sestamibi in plasma. The myocardial blood half-life is approximately six hours after a rest or exercise injection. The biological half-life for the liver is approximately 30 minutes after a rest or exercise injection. The effective half-life of clearance (which includes both the biological half-life and radionuclide decay) for the heart is approximately 3 hours, and for the liver is approximately 30 minutes, after a rest or exercise injection. The ideal imaging time reflects the best compromise between heart count rate and surrounding organ uptake.

Myocardial uptake which is coronary flow dependent is 1.2% of the injected dose at rest and 1.5% of the injected dose at exercise. Table 6.0 illustrates the biological clearance as well as effective clearance (which includes biological clearance and radionuclide decay) of Tc99m Sestamibi from the heart and liver.

[Table 6.0 Biological and Effective Clearance]

A study in a dog myocardial ischemia model reported that Technetium Tc99m Sestamibi undergoes myocardial distribution (redistribution), although more slowly and less completely than thallous chloride Tl-201. A study in a dog myocardial infarction model reported that the drug showed no redistribution of any consequence. In both the biological half-life and approximately thirty-three percent of the injected dose is cleared through the kidneys in 4 hours post dose.

12.3.1 Metabolism

The agent is excreted without any evidence of metabolism.

12.2.2 Elimination

The major pathway for clearance of Tc99m Sestamibi is the hepatobiliary system. Activity from the gall bladder appears in the intestines within one hour of injection. Twenty-seven percent of the injected dose is excreted in the urine, and approximately thirty-three percent of the injected dose is cleared through the feces in 48 hours.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In comparison with most other diagnostic technetium labeled radiopharmaceuticals, the radiation dose to the ovaries (1.5 mrad/30 mCi at rest, 1.2 mrad/30 mCi at exercise) is high. Minimal exposure (ALARA) is necessary in women of childbearing capability. (See Section 2.)

The active intermediate, Cu(II) Bu2Br, was generated for enzymatic potential in a battery of five tests. No genotoxic activity was observed in the Ames, CHO/HIPR and in vitro mammalian chromosomal tests (200 µg/mL). An increase in cells with chromatome aberrations was observed in the in vivo human lymphocyte assays. Cu(II) Bu2Br, did not show genotoxic effects in the in vivo mouse micronucleus test at a dose which caused systemic and bone marrow toxicity (9 mg/kg > 600 x maximal human dose).

14. CLINICAL STUDIES

CLINICAL TRIALS:

MYOCARDIAL IMAGING: In a trial of rest and stress CARDIOLITE imaging, the relationship of normal or abnormal perfusion scans and long term cardiac events was evaluated in 521 patients (511 men, 10 women) with stable chest pain. There were 73.9% Caucasians, 25.9% Blacks and 0.2% Asians. The mean age was 59.6 years (range: 29 to 84 years). All patients had a baseline rest and exercise CARDIOLITE scan and were followed for 13.2 ± 4.9 months (range: 1 to 24 months). Images were correlated with the occurrence of a cardiac event (cardiac death or non-fatal myocardial infarction). In this trial as summarized in Table 7.0, 24/21 (4.6%) had a cardiac event.

<table>
<thead>
<tr>
<th>Table 7.0 Cardiac Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Scan®</td>
</tr>
<tr>
<td>Normal</td>
</tr>
<tr>
<td>Abnormal</td>
</tr>
</tbody>
</table>

(a) Note: Similar findings were found in two studies with patients who had pharmacologic stress CARDIOLITE imaging.

(b) p<0.01

Although patients with normal images had a lower cardiac event rate than those with abnormal images, in all patients with abnormal images it was not possible to predict which patient would be likely to have further cardiac events, i.e., such individuals were not distinguishable from other patients with abnormal images. The findings were not evaluated for defect location, disease duration, specific vessel involvement or intervening management.

In earlier trials, using a template consisting of the anterior wall, inferior-posterior wall and isolated localization in the anterior-or inferior-posterior wall in patients with suspected angina or coronary artery disease was shown. Disease localization isolated to the apex has not been established. In adults, Tc99m Sestamibi has not been studied or evaluated in cardiac disorders other than coronary artery disease.

BREAST IMAGING: MIRALUMA® was evaluated in two multicenter, clinical trials of a total of 673 women patients. Overall the mean age was 52 (range 23 to 87 years). The racial and ethnic representation was 70% Caucasian, 15% African-American, 14% Hispanic and 1% Asian.

Both clinical studies evaluated women who were referred for further evaluation for either: 1) a mammographically detected with varying degrees of malignant likelihood but not palpable breast lesion (study A, n=387, mean age ± 54 years), or 2) a palpable breast lesion (study B, n=606, mean age ± 50 years). In both studies patients were checked periodically.

MIRALUMA® (20 - 30 mCi) was injected intravenously in a vein that was contralateral to the breast lesion in question. Planar imaging was completed with a high resolution collimator with a 10% window centered at 140 KeV and 128 x 128 matrix. An initial marker image, that was not used in the data analysis, was obtained using a cobalt Co57 source as a marker of a palpable mass. Images were obtained 5 minutes after injection as follows: lateral image of the affected breast for 10 minutes, lateral image of the contralateral breast for 10 minutes, and an anterior image of both breasts for 10 minutes. For the lateral image the patients were positioned in a prone position. For the anterior image, the patients were supine. The MIRALUMA® scintigraphic images were read in a randomized method by two groups of three blinded readers. MIRALUMA® uptake was scored as normal (no uptake), focal, high uptake.

The results of MIRALUMA® images and mammaryography were analyzed in comparison to histopathologic findings of malignant or non-malignant disease.

As shown in Table 8.0 for the 483 evaluable patients, the sensitivity and specificity of any degree of MIRALUMA® uptake appear to vary with the presence or absence of palpable mass.

<table>
<thead>
<tr>
<th>Table 8.0 Overall MIRALUMA® Blinded Results of Target Lesions®</th>
</tr>
</thead>
<tbody>
<tr>
<td>STATISTIC</td>
</tr>
<tr>
<td>Number of Patients and Lesions</td>
</tr>
<tr>
<td>Sensitivity</td>
</tr>
<tr>
<td>Specificity</td>
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<tr>
<td>PPV®</td>
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<td>NPV®</td>
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(a) Excludes all discordant lesions not identified at entry and excludes 25 equivalent interpretations from Study A and 25 equivalent interpretations from Study B; (b) Some patients had more than one target lesion.

An estimate of the likelihood of malignancy based on the MIRALUMA® uptake score in combination with the mammographic score has not been studied. In these two studies approximately 150 additional, non-biopsied lesions were found to be positive after MIRALUMA® imaging. These lesions were identified in sites that did not physiologically correlate with identified criteria mammographic lesions and these lesions were not palpable. These lesions were not biopsied. Whether these lesions were benign or malignant is unknown. MIRALUMA® uptake can occur in both benign and malignant disease. THE CLINICAL USEFULNESS OF A POSITIVE MIRALUMA® IMAGE IN THE ABSENCE OF AN ABNORMAL MAMMORAM OR AN ABNORMAL LESION IS NOT KNOWN.

15. REFERENCES

Not applicable.

16. HOW SUPPLIED/STORAGE AND HANDLING

CARDIOLITE®. Kit for the Preparation of Technetium Tc99m Sestamibi for injection is supplied as a 5 mL via in kits of five (5) vials (NDC # 11994-001-55) and twenty (20) vials (NDC # 11994-001-20), sterile and non-pyrogenic.

The patient dose should be measured by a radiolucitivity calibration system immediately prior to patient administration. Radiolucitory purity should be checked prior to patient administration.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Prior to lyophilization the pH is between 5.3-5.9. The contents of the vials are sterilized and stored under nitrogen. Store at 15-25°C (59-77°F) before and after reconstitution.

Technetium Tc99m Sestamibi contains no preservatives. Included in each five (5) vial kit is one (1) package insert, one (1) vial shield labels and six (6) radiation warning labels. Included in each twenty (20) vial kit is one (1) package insert, twenty four (24) vial shield labels and twenty four (24) radiation warning labels. This reagent kit is approved for distribution to persons licensed pursuant to the Code of Massachusetts Regulations 105 CMR 120.500 for the users listed in 105 CMR 120.547 or 120.552, or under equivalent regulations of the U.S. Nuclear Regulatory Commission, Agreement States or Licensing States.

17. PATIENT COUNSELING INFORMATION

CARDIOLITE® and MIRALUMA® are different names for the same drug. Patients should be advised to inform their health care provider if they had an allergic reaction to either drug or if they had an imaging study with either drug.