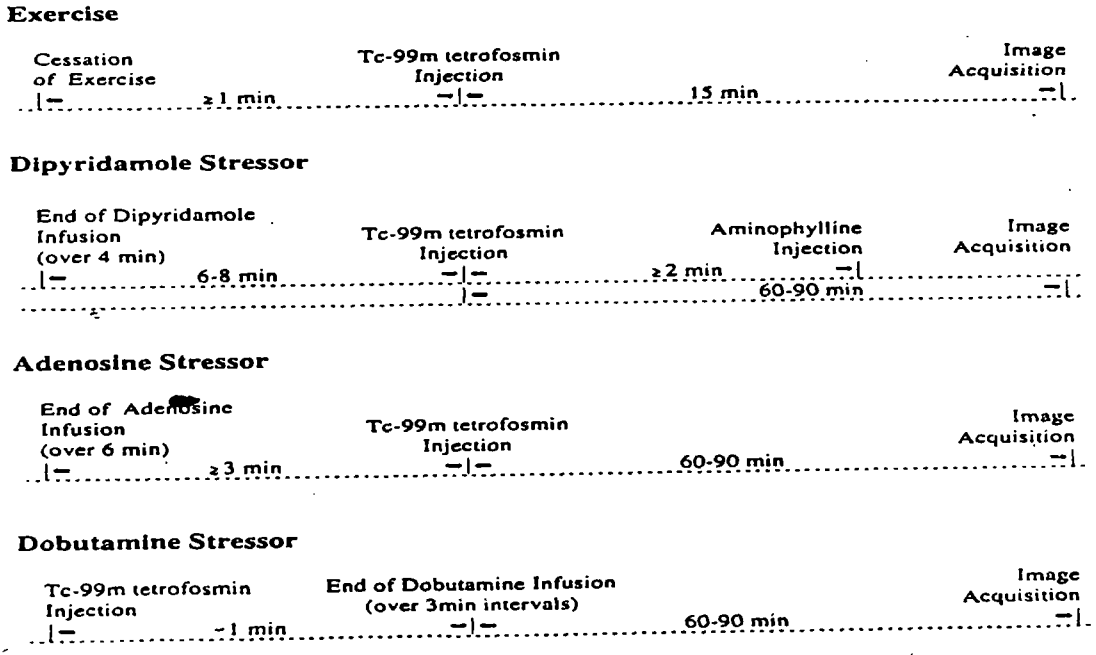
arrhythmia. Tc-99m tetrofosmin, 0.36 mCi/kg intravenous, was to be given at one minute after peak exercise (up to 114 kg. max).

B) Dipyridamole stress protocol: A continuous infusion of 0.56 mg/kg was to be infused over 4 minutes, followed by injection of Tc-99m tetrofosmin (0.36 mCi/kg) at 6 minutes. At 8 minutes, a prophylactic dose of aminophylline, 50-125 mg, was to be given, with additional doses as needed. SPECT was to be performed at 45 minutes after radiopharmaceutical injection.

C) Adenosine stress protocol: A continuous infusion of adenosine, 140 mcg/kg/min was to be given over 6 minutes. Tc-99m tetrofosmin (0.36 mCi/kg) is given at 3 minutes into the adenosine infusion and SPECT acquisition begun 45 minutes later.

D) Dobutamine stress protocol: Dobutamine was to be infused using a pump at an initial rate of 5 mcg/kg/min, increased to 10, 20, 30 and 40 mcg/kg/min at three-minute stages. Continuous 3-lead ECG monitoring, as well as pulse, blood pressure and a 12-lead tracing were to be obtained at each stage. Endpoints for the infusion include: ST depression >4mm, progressive angina, heart rate >85% predicted maximum for age, fall in systolic BP >20 mm Hg, severe hypertension (systolic > 250, diastolic > 130 mm Hg, complex ventricular arrhythmias or supraventricular tachycardias. Atropine was added to the infusion if the increase in heart rate was insufficient (protocol change, Aug. 1996). Myoview (0.36 mCi/kg) was given 1 min. prior to terminating the dubutamine infusion, and SPECT acquisition begun 45 min. later.

FIGURE #1: Time Scale for Myoview Stress Protocols (from p. 56 of submission)



8) IMAGING PROTOCOL: SPECT images of the heart were to be obtained using a SPECT gamma camera. 64 projections of 20 seconds

each will be acquired over a 180 degree arc from RAO to LPO. The images were not to be gated, nor were attenuation/scatter correction algorithms applied. Acquisition parameters are specified in the protocol. Acquisition was to begin 15 to 90 minutes after the injection of Tc-99m tetrofosmin. Filtered back-projection was done using a low-pass Butterworth filter.

9) IMAGE INTERPRETATION AND SCORING: A 17-segment myocardial model, described in the CRF's, was to be used, employing short-axis slices on 3 levels, plus a single vertical-long axis slice. Each segment was to be scored from 0 = normal perfusion to 4 = absent perfusion; for rest and all stress images. Scores from the 17 segments for each image were added to give a total stress or rest score. A "reversibility score" was computed by subtracting the total rest score from the total stress score. Total stress scores <3 were considered normal. The resting images were paired with each stress image, to be interpreted by three observers who would read the images and reach a consensus. These readers were to be blinded as to patient identification, history, stress protocol and previous stress test or image data.

Reviewer's comment: Two inconsistencies re. scoring were evident: 1) there is no definition of a segmental score of 5 (page 61), and 2) the CRF indicates a score of 0 to represent absent perfusion (or is it absent uptake?). (page 176, vol. 2)

10) STATISTICAL METHODS: Data for each case was to be reported in Case Report Forms supplied by the sponsor. Demographic and dosing information were to be analyzed using descriptive statistics. For safety data, all 49 subjects (including volunteers with low CAD probability) were to be analyzed. For efficacy, statistical methods chosen to compare the data from the resting and four stress test results include the repeated-measures analysis of variance. A p-value of <0.05 was considered significant. The Tukey honesty significant difference test was to be applied, and the sample size of 25-30 patients and 10 normal subjects was estimated to be adequate for this study.

11) SAFETY CONSIDERATIONS: See Study Flow Chart, Table #1.

A) Adverse events: Monitoring was planned for the duration of the study (which was not clearly specified). These were to be reported in the CRF with description, date of onset, seriousness, relationship to Myoview or stress agent injection and duration/resolution.

B) Vital signs: The CRF called for vital sign (heart rate, systolic and diastolic blood pressure) measurements at the time of each stress test (exercise or pharmacologic); for baseline and peak measurements. Changes from baseline of >20 mmHg or >15 bpm were considered significant.

C) A 12-lead ECG was to be obtained at baseline prior to each stress test and at 2-minute intervals during the tests. Continuous 3-lead monitoring was also carried out during exercise and pharmacologic stress. Distributions of ST-segment deviations were recorded and analyzed.

D) Laboratory evaluation: Laboratory tests were not included in the protocol.

12) STUDY RESULTS

A) Demographics and Baseline Characteristics

The protocol called for enrollment of 25-30 patients and 10 healthy volunteers at one institution; 49 were ultimately enrolled. Ten patients were withdrawn from the study and one lost to followup. Table #2 summarizes the demographic information for the 49 patients in Study #PR96-301.

TABLE #2: DEMOGRAPHIC CHARACTERISTICS (from p. 68 of submission)

Characteristic	N = 49	Characteristic	N = 49
Age: Mean	58.70	Height (cm): Mean	68.18
SD	11.50	SD	3.06
Range	33.9-81.1	Range	59.0-74.0
Race: White	35 (71%)	Weight (kg): Mean	82.33
Black	3 (6%)	SD	13.69
Hispanic	10 (20%)	Range	56.8-117.2
Other	1 (2%)		
Gender: Male	44 (90%)		
Female	5 (10%)		

B) Deviations from the protocol as written were listed on page 65-67. These include changes in the statistical analysis methods: analysis of variance for a mixed model to compare the four stress SPECT scores in CAD patients, and paired t-tests to evaluate the degree to which each pharmacologic stress agent SPECT result differed from those of exercise stress in CAD patients. The healthy volunteers' results were analyzed separately.

C) Baseline Cardiac and Medication History (p. 68 of submission)

Tabulations were made for every subject's baseline cardiac history, and risk factors, including angina, previous MI, CABG, PTCA or other cardiac catheterization. Cardiac risk factors were also listed. The above data was presented for both CAD patients (31 subjects) and subjects chosen for low CAD risk (7 subjects).Table #3 summarizes the cardiac history information.

TABLE #3: CARDIAC HISTORY (from table #10:3B, p. 68 of submission)

Cardiac History	CAD patients (N=31)	Non-CAD volunteers (N=7)
Angina pectoris	25 (81%)	1 (14%)
Previous MI	18 (58%)	0
Previous angiogram	22 (71%)	1 (14%)
Previous CABG	8 (26%)	0
Previous PTCA	1 (3%)	0

D) Dosage and Administration

Forty-eight (48) subjects were given at least one dose of Myoview; one was not dosed as he developed leg pain during exercise. Ten subjects withdrew from the study after exercise stress; one was lost to followup, leaving 38 subjects to undergo all four stress tests (and Myoview injections). Table #4 lists the Myoview dose in mCi and mCi/kg for all four stress tests.

TABLE #4: DRUG EXPOSURE (Table #10.5, p. 69 of submission)

Table 10.5
Summary of Dosing Information

Tc-99m Tetrofosmin Dosing Parameter	Stress/Rest Condition				
	Exercise [a]	Rest [b]	Adenosine	Dipyridamole	Dobutamine
Dose, mCi					
N	48	48	39	39	38
Mean	28.11	28.03	29.34	29.01	29.04
SD	3.08	2.97	3.24	4.02	3.85
Range (min, max)					
Dose, mCi/kg					
N	48	48	39	39	38
Mean	0.35	0.35	0.36	0.35	0.35
SD	0.05	0.05	0.05	0.04	0.04
Range (min, max)					

[a] One subject (#10) developed leg pain during exercise stress and thus did not receive Tc-99m tetrofosmin.
[b] One subject (#8) completed the exercise stress study but was then lost to follow-up.
REF: Sections 15.1.4 and 16.2.4.2

E) Safety Results

1) Adverse Events:

There were no deaths but serious adverse events caused two subjects to withdraw from the study following the exercise stress test. According to the table below, 44 of the 49 evaluable patients receiving Myoview (90%) experienced a total of 170 adverse events in this phase 3 trial. Event occurrences were tabulated for each stress agent and exercise; in general, AE's were more frequent with pharmacologic stress, especially adenosine. According to the sponsor, no apparent relationship was seen between the administration of Myoview and any of the adverse events. All adverse events were attributed to exercise or the pharmacologic stress agents by the investigators.

The most common adverse events were angina pectoris (23/49 or 47%), flushing (23/49 or 47%) and headache (-20/49 or 41%), as shown in table #5. No relationships between adverse events and age and race were noted. During Myoview stress tests, - patients received aminophylline (mean - mg, range -- mg).

Both serious adverse events occurred during the exercise test. The first patient (Subject #24, developed ischemic changes on ECG similar to that experienced on 2 previous stress tests. The second patient, #37,

developed ventricular tachycardia which spontaneously resolved when exercise was stopped. Both were withdrawn from the study.

TABLE #5: NUMBER OF PATIENTS WITH ADVERSE EVENTS
(derived from p. 74 of submission)

Body System	Event Type N, (%)	Exercise (N=49)	Dipyrida-mole (N=39)	Adeno-sine (N=39)	Dobuta-mine (N=38)	Combined (N=49)
	Any event	17 (35)	27 (69)	38 (97)	31 (82)	44 (90)
Body as a Whole	Headache	9 (23)	15 (38)	9 (23)	3 (8)	20 (41)
	Flushing	0 (0)	6 (15)	20 (51)	4 (11)	23 (47)
	Leg pain	5 (10)	1 (3)	0 (0)	0 (0)	6 (12)
Nervous	Dizziness	1 (2)	4 (10)	2 (5)	0 (0)	4 (8)
	Paresthesia	0 (0)	0 (0)	4 (10)	1 (3)	5 (10)
Cardio-vascular	Angina	5 (10)	7 (18)	18 (46)	10 (26)	23 (47)
	Palpitation	0 (0)	0 (0)	2 (5)	11 (29)	13 (27)
	Arrhythmia	0 (0)	0 (0)	0 (0)	2 (5)	2 (4)
	Vent. arrhyth.	2 (4)	0 (0)	0 (0)	1 (3)	3 (6)
Pulmonary	Dyspnea	6 (12)	1 (3)	6 (15)	2 (5)	12 (24)
Digestive	Nausea	0 (0)	0 (0)	2 (5)	1 (3)	2 (4)

Reviewer's comments: 1) No information was given regarding patients taking aminophylline to counteract adverse events arising from dipyridamole.
2) The sponsor needs to clarify if the category "arrhythmia" above pertains only to supraventricular cases.

2) Vital Signs: (Summarized in Table #6 on next page)

Vital signs (heart rate, systolic BP and diastolic BP) were recorded as baseline and maximal values, for exercise and the three pharmacologic stress agents. For each measurement, mean and standard deviation as well as the difference and p-value for change from baseline, was recorded. Changes outside a specified range (>15 bpm for heart rate, >20 mm Hg for blood pressure) were also recorded and tabulated. For exercise and dobutamine stress, the greatest number of changes of BP and pulse outside the specified range occurred:

a) For pulse, all 49 subjects had increases of >15 bpm for exercise and 37/38 had increases of >15 bpm for dobutamine. For dipyridamole and adenosine, 22/39 and 26/39 increased the pulse by >15 bpm, respectively. There were no decreases of >15 bpm.
b) For systolic blood pressure during exercise, 34/49 had increases and none had decreases of >20 mm Hg. For dobutamine, 21/38 increased and 1 decreased systolic BP by >20 mm Hg. For dipyridamole and adenosine, 2/39 and 1/39 increased BP by >20 mm Hg, respectively.

None of 39 subjects decreased systolic BP by >20 mm Hg for dipyridamole; two decreased by > 20 mm Hg for adenosine.

c) For diastolic BP, no subjects increased by >20 mm Hg for any stress agent or exercise; only 1/39 decreased by >20 mm Hg for adenosine.

TABLE #6: VITAL SIGNS (From p. 76 of submission) (mean and SD)

Stressor	Heart rate (bpm)	Systolic BP (mm Hg)	Diastolic BP (mm Hg)
EXERCISE			
Baseline	72.8 (12.3)	132.6 (20.6)	73.7 (9.1)
Maximum	152.4 (19.1)	163.0 (19.3)	77.2 (8.5)
Difference	79.6 (18.5)	30.4 (19.5)	3.5 (9.1)
P-value	0.0001	0.0001	—
DIPYRIDAMOLE			
Baseline	69.5(11.6)	131.9(20.0)	73.1(7.6)
Maximum	86.9 (13.7)	131.8 (18.0)	72.3 (8.3)
Difference	17.5 (7.5)	-0.1(10.9)	-0.8(6.3)
P-value	0.0001	0.9768	—
ADENOSINE			
Baseline	70.8(13.1)	132.9(14.5)	75.2(8.4)
Maximum	91.8(15.0)	130.9(13.8)	71.8 (10.0)
Difference	21.0(9.7)	-2.0(13.0)	-3,4 (8.9)
P-value	0.0001	0.3366	—
DOBUTAMINE			
Baseline	69.0(11.9)	132.6(16.4)	75.9(8.2)
Maximum	131.4(18.4)	156.8 (30.9)	72.4(11.3)
Difference	62 5 (18.6)	24.2(25.7)	-3.5 (8.8)
P-value	0.0001	0.0001	—

In general, changes in BP and heart rate reflected the stress agents used; dobutamine and exercise were similar in producing the large number of increases above the preset amounts. Likewise, adenosine and dipyridamole were similar in that few changes outside the specified magnitude were seen.

3) ECG's:

ST-segment deviations in 0.5 mm increments were recorded for peak stress for the three stress agents as in Table #7 on the next page. ST-segment changes were not measured for the exercise test, which is unfortunate since ST changes are part of routine treadmill ECG exercise testing. As in Study # PR95-302 and P53-006, QT and QTc intervals as well as other ECG parameters were not recorded. Dobutamine produced the most significant ST changes among the three stressors.

TABLE #7: ST-Segment Changes with Stress (from Table #12.6, p. 77)

ST-segment changes	Dipyridamole (N=39)	Adenosine (N=39)	Dobutamine (N=38)
<0.5 mm	36/39 (92%)	32/39 (82%)	16/38 (42%)
0.5-1.0 mm	1/39 (3%)	3/39 (8%)	14/38 (37%)
1.0-1.5 mm	2/39 (5%)	1/39 (3%)	4/38 (11%)
1.5-2.0 mm	0	1/39 (3%)	2/38 (5%)
>2.5 mm	0	0	2/38 (5%)
Missing data	0	2/39 (5%)	0

Reviewer's comments: 1) The QT interval (or QTc) was not reported in the tables; it is an important measure of toxicity and should be part of the safety database for Myoview.

2) St-segment changes are part of routine exercise stress testing; the sponsor needs to explain why they were not obtained here.

F) Efficacy Results

The evaluation of efficacy in this study addressed the endpoints of myocardial perfusion and quantitative scoring of defects seen on Myoview SPECT scintigraphy, in a database from 38 subjects (31 had diagnosed CAD; 7 were considered healthy volunteers; the two groups were analyzed separately). These parameters were compared for exercise and three different pharmaceutical stress agents. Unlike Studies #PR 95-302 and P53-006, this investigation was not intended to compare the ability of Myoview scintigraphy to detect CAD with a gold standard (coronary angiography). As such, it was not intended to provide pivotal support to extending the indications of Myoview to include scintigraphy of the myocardium in the setting of pharmacologic stress.

1) Stress and Reversibility SPECT Scores: The scoring system for SPECT scans is described in Section #9 of this review. For the 31 CAD subjects, a significant difference was seen between stress SPECT scores for exercise when compared to dipyridamole (p=0.012). Reversibility scores showed significant differences from exercise for both dipyridamole (p=0.003) and dobutamine (p=0.02). For adenosine, the difference did not reach significance for either stress or reversibility scores.

TABLE #8: SPECT Scores (reproduced from Table #11.3.1, p. 71)

Table 11.3.1
Total Stress and Reversibility SPECT Scores

Stress Condition	CAD Subjects (N=31) Mean (SD)				Non-CAD Subjects (N=7) Mean (SD)	
	Stress Score	P-Value	Reversibility Score	P-Value	Stress Score	Reversibility Score
Exercise [a]	13.9 (8.2)	—	7.3 (3.9)	—	1.4 (2.6)	1.3 (2.6)
Dipyridamole	11.8 (9.2)	0.012	4.9 (4.1)	0.003	0.9 (1.9)	0.9 (1.9)
Adenosine	13.4 (9.6)	0.49	6.1 (3.8)	0.07	0.4 (0.8)	0.3 (0.8)
Dobutamine	12.3 (9.0)	0.06	5.5 (3.8)	0.02	0.0 (0.0)	0.0 (0.0)

[a] Exercise serves as reference condition.

SD = standard deviation.

For non-CAD subjects, stress and reversibility SPECT scores for exercise and the 3 stress agents were not significantly different.

2) Abnormal SPECT Score Responses: An abnormal response of a patient's SPECT score was defined as a total exercise stress score of >3. Exercise stress produced abnormal responses in 30/31 (97%) of the subjects with CAD. Of these 30, 25 (83%) had an abnormal response to dipyridamole, 28 (93%0 to adenosine and 27 (90%) to dobutamine stress. For the 7 subjects without CAD, one had an abnormal response to exercise and one (a different patient) to dipyridamole stress. All had normal responses to dobutamine and adenosine.
3) SPECT Scores by Response Groups: The 31 subjects with CAD were divided into three "response groups" based on stress defect scores with exercise: low = 3 to 8; medium = 9 to 14, and high = 15 and above For all three groups, the mean total defect score was lower for the subsequent pharmacologic agents than exercise, with the exception of dobutamine for the medium group. The sponsor concludes from these data that pharmacologic stress studies are not more likely to miss mild perfusion defects nor underestimate severe ones than exercise stress.
Reviewer's comment: It appears that cutoff levels for "response groups" among the CAD subjects were chosen arbitrarily.

13) SPONSOR'S CONCLUSIONS (extracted from p. 81, vol. 2 of submission)

- Tc99m tetrofosmin showed no significant differences in detecting the presence, extent, and seventy of myocardial perfusion defects with the pharmacologic stress agents adenosine and dobutamine when compared with exercise in subjects with known CAD.
- There was significant difference in detecting reversibility with dobutamine, probably due to the slightly fewer subjects demonstrating abnormal stress images as well as the slightly fewer demonstrating reversibility of these defects.
- The apparent slight but significant difference in myocardial perfusion defect results seen between dipyridamole pharmacologic stress and exercise images most likely is due to the early reversal of vasodilatation by aminophylline, resulting in less time for Tc99m tetrofosmin uptake during stress perfusion conditions. A difference in efficacy between dipyridamole and adenosine may also be a factor.
- In the low-likelihood for CAD subjects, Tc99m tetrofosmin demonstrated essentially normal perfusion images with all three pharmacologic stress agents. These results were comparable to those obtained with exercise stress.
- There was no evidence for a marked plateau effect with any of the pharmacologic stress agents.
- There were no serious adverse events noted in any subject with any pharmacologic stress agent; the frequency and type of adverse events seen with each stress agent in this study were similar to those noted in the package insert and in the literature for the respective agents. There were no adverse events attributed to Tc99m tetrofosmin.
- The heart rate and blood pressure changes noted were consistent with those known to occur with each pharmacologic stress agent used in this study.

14) REVIEWER'S COMMENTS

A) Trial design and protocol execution:

The design of this trial, a single-center, open-label, comparative type, was appropriate for this Phase 3 investigation. The protocol was generally followed, though a number of changes were made (all listed on page 65-66 of the submission). The majority of these changes involved the statistical analysis methods for the efficacy data. There were ten subject dropouts from the efficacy analysis, all post-exercise stress; all 49 subjects were included in the safety database. Unfortunately, the sample size is small to begin with. The study utilized blinded reading of SPECT images for primary efficacy assessment, though interpretation was by consensus of the three blinded readers rather than independent reads. A more detailed study timetable would have made it easier to follow the overall study plan.

B) Safety and adverse events results:

As Myoview is already approved for use with exercise testing in the diagnosis of CAD, the sponsor felt it was unnecessary to monitor laboratory (hematology, chemistry and urinalysis) or pulse oximetry. Nevertheless, the quality of the safety database could be improved. A number of specific questions have been raised during review of this study report:

1) It is not clear how long patients were to be followed for adverse events after injection of Myoview.
2) Since rest imaging was done first, it would be possible to differentiate AE's related to dipyridamole plus Myoview from those related to Myoview alone (unlike in Study # P53-006).Such an analysis was not undertaken.
3) The sponsor also needs to analyze vital signs and ECG's after the rest injection of Myoview, and compare these to those obtained after the post-exercise and pharmacologic stress Myoview injections.
4) The QT interval (or QTc) on the electrocardiogram was not reported in the tables; it is an important measure of drug toxicity and should be part of the safety database for Myoview.
5) It is unfortunate that the sponsor did not report ST-segment changes with the exercise tests.
6) Patients undergoing treatment for bronchospasm or taking theophylline compounds should have been in the exclusion criteria.
7) No information was given about patients being given aminophylline to counteract adverse events arising from dipyridamole.
8) Two serious AE's were reported, but not included in the discussion (p.80)
9) Shift tables and scatter plots of safety data would be very helpful.

C) Efficacy results:

1) A consensus interpretation of SPECT images is not as credible as independent reads, even if performed by blinded readers.

2) The sponsor has provided no formal assessment of image quality in this study.
3) There is no report or analysis of the adequacy of exercise (percent of predicted maximal heart rate, double product etc). Since exercise is the "standard of truth" against which pharmacologic stress is compared in this study, such information would be useful.
4) Two inconsistencies in defect scoring were evident: 1) there is no definition of a segmental score of 5 (page 61) and 2) the CRF indicates a score of 0 to represent absent perfusion (or is it absent uptake?). (page 176 of submission)
5) It appears that cutoff levels for "response groups" among the CAD subjects undergoing stress Myoview scans were chosen arbitrarily.

D) Reviewer's conclusions: Study #PR96-301 was conducted by the sponsor with the intention to compare the effect of different types of stress upon myocardial uptake of Myoview and its ability to delineate perfusion defects in patients with CAD. As such, it was not intended to provide pivotal support to the indication of Myoview for myocardial scintigraphy in the setting of pharmacologic stress. Nevertheless, the sponsor has tried to demonstrate that a given patient with myocardial ischemia will have perfusion defects which are similar with exercise stress or pharmacologic stress. The stress perfusion defects were in fact not statistically different between exercise and adenosine or dobutamine, but were smaller when dipyridamole was used. The sponsor explains this as possibly due to a protocol flaw, where prophylactic aminophylline is begun too soon after injection of Myoview. This would result in inadequate tracer uptake by the myocardium at the time dipyridamole-induced vasodilatation is reversed by aminophylline; and less apparent perfusion defects. As for safety, the two serious AE's appear to be related to exercise and not Myoview, and the adverse event/vital sign/ECG profiles of the three stress agents reflected the pharmacologic effects of the respective agents.

APPENDIX 4: CLINICAL REVIEW OF LITERATURE STUDIES sNDA #20,372
Non-pivotal Studies
Clinical Review of Literature Study: Fukuzawa 1996 (pp.1794-1798, vol. 7)

Study Title: "Tc-99m tetrofosmin myocardial perfusion SPECT after dipyridamole combined with low level exercise in the diagnosis of coronary artery disease"
Authors: Fukuzawa, Ozawa, Innagaki, Inoue, Morooka, Sugioka
Trial center: Funabashi Municipal Medical Center, Chiba, Japan
Reference: ***Annals of Nuclear Medicine*** 10, no. 2, 1996, pp. 231-235

1) STUDY OBJECTIVES: "to determine the clinical value for myocardial perfusion Tc-99m tetrofosmin imaging after dipyridamole combined with low level exercise in the diagnosis of coronary artery disease" (quote, p. 1795, vol. 7)

2) STUDY DESIGN: This study is a single-center, open-label, double-administration, non-randomized prospective trial where Tc-99m tetrofosmin scintigraphy in the setting of pharmacologic and low-level exercise stress is compared to coronary angiography as a truth standard. Subjects were given a 4-minute infusion of dipyridamole followed by 3 minutes of low-level bicycle exercise. At peak stress, 8 mCi of Tc-99m tetrofosmin was injected IV, followed by SPECT imaging. Four hours later, subjects underwent rest SPECT with 24 mCi. Tc-99m tetrofosmin. Efficacy endpoints included sensitivity of tetrofosmin SPECT for detecting 1, 2 and 3-vessel CAD; sensitivity, specificity, diagnostic accuracy and predictive values for stenoses of each of the 3 major vessels, and ability to predict the severity of CAD through determining the number of areas of abnormal myocardial Tc-99m tetrofosmin uptake. There was no formal safety assessment except for vital signs, adverse events and ECG monitoring during stress testing.

3) STUDY TIMETABLE: A timetable was not provided for the overall study, but stress/rest injection/imaging protocols were schematized.

4) PATIENT POPULATION: 42 patients with stable CAD and 10 healthy volunteers
   A) Inclusion criteria: Patients with CAD must have > 50% stenosis of at least 1 vessel on angiogram, and be unable to exercise fully due to physical disabilities which were listed.
   B) Exclusion criteria: Well-documented prior MI, LBBB, significant valvular disease, unstable angina and cardiomyopathy.

5) PRESTUDY PREPARATION: Patients were asked whenever possible to stop routine medications at least 24 hours before testing. Coronary angiography was done "several days" before Myoview scanning. Stenoses were measured by an automated edge-detection method.

6) DOSAGE AND ADMINISTRATION: The protocol called for the dose of 296 mBq (8.0 mCi) of Myoview to be given at stress and 888 mBq (24 mCi) at rest. The dose of

dipyridamole was to be 0.142 mg/kg/min I.V. over 4 minutes, followed immediately by 3 minutes of supine low-level (25 watt) bicycle exercise.

7) IMAGE ACQUISITION AND INTERPRETATION: SPECT of the myocardium was acquired beginning 36 minutes after the 8 mCi stress Myoview dose (20% window at 140 KeV). Following acquisition, images were processed using a Ramp filter and filtered back projection. The resulting transaxial images were reconstructed in the 3 cardiac axes. The slices were then divided into segments (not specified or illustrated in article). Visual inspection was used to determine if perfusion to a segment was decreased; 2 adjacent decreased segments was considered abnormal. Side-by-side rest and stress images were then assessed for reversibility. Segments were assigned a coronary territory for subsequent correlation with angiography.

8) CORRELATIVE IMAGING: Coronary angiography was done "several days" before Tc-99m tetrofosmin scanning. Measurement was by automated edge-detection methods. Stenoses of >50% were considered significant, and >70% severe.

9) SAFETY EVALUATIONS were limited to recording of adverse events, ECG and pulse and systolic blood pressure during pharmacologic and exercise stress.

10) BLINDING AND METHODS TO MINIMIZE BIAS: Three investigators read the images and reached a consensus. They were blinded as to angiography results.

11) EFFICACY ANALYSES AND STATISTICAL METHODS:
   A) Safety data: Hemodynamic (systolic BP and pulse) values were reported as mean ± standard deviation for rest, post-dipyridamole and peak stress values.
   B) Efficacy data: Descriptive statistics were reported for the relationship between scintigraphic and angiographic findings (sensitivity, specificity, predictive values and accuracy). The Student's T-test was used for paired and unpaired values; the chi-square was used for comparison of categorical variables.

12) STUDY RESULTS
   A) Demographics and Baseline Characteristics

   42 patients with CAD and 10 healthy volunteers were enrolled; no mention was made of withdrawals from the study. The patients' mean age was 62.4 ± 2.8 years; that of the healthy controls was 38.6 ± 2.4 years. No range was given. 71% of the patients and 70% of controls were male.

   B) Safety Results: Chest pain was experienced by 7 patients (13.5%); headaches and nausea by 4 patients (7.8%). No subject received aminophylline, but two received sublingual nitroglycerin. The means and standard deviations were given for heart rate and systolic BP during dipyridamole infusion: heart rate rose from 68 ± 14 to 82 ± 12 bpm with dipyridamole infusion, and reached 101 ± 16 at the time of Myoview injection. Systolic BP fell from 152 ± 30 to 128 ± 32 mmHg with dipyridamole infusion, and reached 164 ± 38 mmHg at the time of Myoview injection. Ischemic ST-T changes were seen in 6 patients (11.1%).

C) Efficacy Results

The evaluation of efficacy in this study comprised a measure of sensitivity, normalcy rate and diagnostic accuracy of Tc-99m tetrofosmin SPECT for diagnosing 1, 2 and 3-vessel CAD; and the ability of SPECT to predict severity of CAD by correlating number of regions with abnormal perfusion with angiographically stenosed arteries.

Images were described as "Good" in all 52 patients and volunteers studied (criteria not specified). Overall, 35 of 42 patients with documented CAD were found to have an abnormal Myoview SPECT study (sensitivity = 83.3%). Overall sensitivity was also reported with diseased vessels as the denominator: for 50% or greater stenoses, 48 of 66 vessels (72.7%) were positive on Myoview scan; for 70% or greater stenosis, 31 of 36 vessels were positive on Myoview (86.1%). Ten of 10 normal volunteers had normal studies (normalcy rate = 100%). Statistics for each of the coronary arteries are listed in the table below (from #4 in article).

TABLE #1: Diagnostic Accuracy for Each Vessel

STATISTIC	LAD	LCx	RCA
Sensitivity	83%	47%	75%
Specificity	92%	88%	91%
Positive predictive value	96%	73%	89%
Negative predictive value	71%	71%	83%
Overall accuracy	86%	72%	83%

By comparing angiographic stenoses with regions of decreased Myoview uptake, the authors attempted to predict CAD severity in each of the 52 patients. Only sensitivity was reported (83.3% for 1, 2 and 3-vessel disease as well as the diseased population as a whole). The number of diseased vessels is compared to number of abnormal myocardial segments in Table #2 below (reproduced from #5 in article). The correct extent of disease (# of diseased vessels) was predicted in 36 of 52 patients (69.2%), while disease severity was underestimated in 13/52 (25.0%), and overestimated in 3/52 (5.8%). Noteworthy is the underprediction of 3-vessel disease: SPECT demonstrated no involvement in one patient and 1-vessel involvement in two. Only 2 of 6 (33.3%) of 3-vessel disease patients had all 3 vessels abnormal on Myoview SPECT.

TABLE #2: Prediction of CAD Extent

Number of stenosed vessels	Number of abnormal Myoview SPECT regions				
	0	1	2	3	Total
0	10	0	0	0	10
1	4	17	3	0	24
2	2	3	7	0	12
3	1	1	2	2	6

13) AUTHOR'S CONCLUSIONS: "Tc-99m tetrofosmin SPECT, after dipyridamole infusion combined with low-level bicycle exercise, is a valuable diagnostic tool for the evaluation of coronary artery disease."

14) REVIEWER'S COMMENTS:

A) Design strengths: The study has several strengths with respect to design and reporting of methodology and results. Patients (and healthy volunteers) were enrolled prospectively (inclusion and exclusion criteria were specified), and there was a detailed description of dosing, acquisition and processing procedures. The study evaluated Myoview SPECT against coronary angiograms as a truth standard. Importantly, SPECT readers were blinded to angio results (though reading was by consensus of the 3 interpreters). To allow for different criteria for "significant" stenoses, the authors analyzed results "by patient", and "by vessel", and using two levels of stenosis severity (50% and 70%).

B) Design limitations: Several deficiencies decrease the supportive value of this paper. The sample size was small (42 patients, 10 normal volunteers), though this study is more robust than some conducted by the sponsor. The age range between patients and controls was not matched, and the time between angiography and Myoview scanning was not clearly indicated ("several days"). The use of low-level bicycle exercise combined with dipyridamole unfortunately renders this study unable to evaluate the efficacy of Myoview scintigraphy using dipyridamole alone as a substitute for exercise stress.

The manuscript did not specify or illustrate the regions into which the myocardium was subdivided; a "segment-by-segment" analysis of efficacy was not done. Furthermore, there was no mention of criteria for decreased myocardial uptake of the tracer within a given segment, or methodology for "normalization" of tracer uptake. A consequence of this is that a segment-by-segment meta-analysis with other studies in the submission is now impossible.

The criteria for image quality were not defined, but only described as "good".

No mention if readers were blinded to patient history as well as angiographic results. Readers of the angiograms ideally should also be blinded to history and Myoview scan results, but no mention was made of this. Furthermore, an independent blinded read carries more weight than one done by consensus.

Specificity, PPV and NPV were not reported for CAD patients as a whole, but only for each coronary artery.

C) Reviewer's conclusions:

The results show a fairly acceptable sensitivity for the technique for diagnosing CAD overall, and for the LAD and RCA. Sensitivity was poor for the LCx at 47%. Unfortunately, sensitivity for detecting 3-vessel CAD is also poor, most likely the result of "balanced ischemia" in two or more adjacent territories. As a result, CAD severity was under-estimated in 13/52 (25%) of patients with known disease, and in 4/6 (66%) of those with 3-vessel disease.

The use of low-level bicycle exercise unfortunately renders this study unable to support an efficacy claim for Myoview scintigraphy using dipyridamole alone as a substitute for exercise in the diagnosis of CAD or myocardial ischemia.

Clinical Review of Literature Study: Adachi 1995 (pp. 1756-1777, vol. 7)

Study Title: "Clinical Usefulness of Dipyridamole Loading Tc-99m Tetrofosmin Myocardial Scintigraphy"
Authors: Adachi, Sugioka, Tabuchi, Namba, Nakata, Nishigaki, Matsui, Sueyoshi, Narabayashi, Ohkubo, Tamoto, Ohtake
Trial center: Dept. of Radiology, Osaka Medical College, Osaka, Japan
Reference: **Translated from the Japanese literature**

1) STUDY OBJECTIVES: This study was conducted to determine optimal dosage and imaging time for myocardial perfusion Tc-99m tetrofosmin imaging using dipyridamole in the diagnosis of coronary artery disease, and assess the "usefulness" of such imaging as compared to coronary angiography.

2) STUDY DESIGN: This study is a single-center, open-label, double-administration, non-randomized trial evaluating Tc-99m tetrofosmin scintigraphy in the setting of pharmacologic stress in 107 patients with suspected heart disease. Comparison is made to coronary angiography as a truth standard in a subset of 55 patients. Subjects were given a 4-minute infusion of dipyridamole (0.56 mg/kg). At peak stress, 5 or 7 mCi of Tc-99m tetrofosmin was injected IV, followed by SPECT imaging 15 to 60 minutes later. Three hours later, subjects were given 15 mCi Tc-99m tetrofosmin, followed 60-90 minutes later by rest SPECT. Efficacy endpoints included sensitivity of tetrofosmin SPECT for detecting single- or multivessel CAD and disease of each vessel, as well as comparisons of perfusion abnormalities with wall motion abnormalities seen on contrast left venticulography. Safety information was not provided.

3) STUDY TIMETABLE: A timetable was not provided for the overall study, but stress/rest injection/imaging protocols were schematized.

4) PATIENT POPULATION: 107 patients with a history of cardiac disease
   A) Inclusion criteria: Randomly selected patients with a history of cardiac disorder
   B) Exclusion criteria: Subjects without a history of heart disease.

5) PRESTUDY PREPARATION: Patients were asked to fast before testing. The time between coronary angiography and Myoview scanning was not given.

6) DOSAGE AND ADMINISTRATION: The protocol called for the dose of 185 mBq (5.0 mCi) of Myoview to be given at stress and 555 mBq (15 mCi) at rest. The stress dose was raised to 259 mBq (7 mCi) after stress images in the first 36 cases were found to be of poor quality. The dose of dipyridamole was to be 0.14 mg/kg/min I.V. over 4 minutes, followed 3 minutes later by the first Myoview dose. At approx. three hours (range 2.5 to 3.5 hours) after the first dose of Myoview, the second dose (555 mBq, 15 mCi) was given, and the patient fed a meal.

7) IMAGE ACQUISITION AND INTERPRETATION: SPECT of the myocardium was acquired beginning 15 to 60 minutes after the 5 or 7 mCi stress Myoview dose and 60 to 105 minutes after the resting 15 mCi dose. Following acquisition, images were processed using a Siemens ZLC 7500 gamma camera, Shepp-Logan filter and filtered back projection. The resulting transaxial images were used to obtain slices in the three cardiac axes. The slices were then divided into six segments (anterior, posterior, lateral, apical, inferior and septal). Image quality was evaluated as 1 = poor, 2 = moderate or 3 = excellent, while overlapping of liver and cardiac uptake was graded as 1 = severe, 2 = mild or 3 = none. Visual inspection was used to determine if perfusion to a segment was decreased. Uptake of the tracer in a segment was scored 0 = none, 1 = severely reduced, 2 = mildly reduced, 3 = normal and 4 = increased uptake. Side-by-side rest and stress images were then interpreted to assess reversibility. Segments were assigned a coronary territory for subsequent correlation with angiography.

8) CORRELATIVE IMAGING: Coronary angiography and left ventriculography was performed to assess coronary stenoses and wall motion. A stenosis of 75% was considered significant. Wall motion was scored as 0 = dyskinesis, 1 = akinesis, 2 = hypokinesis and 3 = normal motion. Unfortunately, the catheterization results were not reported. The time period between SPECT and angiography was also not indicated. No thallium-201, RVG or other myocardial scintiscans were obtained.

9) SAFETY EVALUATIONS were not described in the paper or sponsor's summary.

10) BLINDING AND METHODS TO MINIMIZE BIAS: Two investigators read the images and reached a consensus. No mention was made of blinding the readers with respect to history or contrast coronary angiography results.

11) STATISTICAL METHODS:
A) Safety data: No data was provided.
B) Efficacy data: Sensitivity was reported for Myoview scintigraphy with the angiographic findings as a truth standard. Wall motion abnormalities on left ventriculography were correlated to segments with decreased Myoview uptake. Otherwise, no formal statistical analyses were presented.

12) STUDY RESULTS
A) Demographics and Baseline Characteristics

107 patients with a cardiac disorder were enrolled; no mention was made of withdrawals from the study. Of these, 79 (74%) were male, 28 (26%) were female. The patients' mean age was 59 $\pm$ 13 years. No range was given.

Of the 107 patients, 37 (35%) had a previous myocardial infarction, 51 (48%) had suspected angina pectoris, 7 (7%) had both an MI and suspected angina and 12 (11%) had cardiomyopathy or other cardiac disease.

Fifty-five of the 107 patients (51%) underwent coronary angiography and form the basis for assessing the efficacy of Myoview. Among these, 26 (47%) had a prior MI, 26 (47%) had angina and 3 (6%) had both.

B) Efficacy Results

The evaluation of efficacy in this study comprised a semiquantitative assessment of image quality and overlap of cardiac and hepatic tracer activity, and a measure of sensitivity of Tc-99m tetrofosmin SPECT for diagnosing single- or multivessel CAD. Coronary angiography was used as a truth standard, but for only 55 of the 107 patients enrolled. Unlike in other literature articles in this submission, a significant stenosis was 75% or more, and wall motion on left ventriculography was also compared with decreased segmental Myoview uptake.

The delayed images obtained with 15 mCi (555 mBq) of Myoview were described as "Good" (criteria not specified) in all patients studied. With the stress images, the quality score was better (2.8 $\pm$ 0.5 vs. 2.4 $\pm$ 0.8) with 7 mCi than 5 mCi of the tracer, though the difference was not statistically significant. Hepatic overlap scores were also not significantly changed by the higher dose (2.2 $\pm$ 0.9 vs. 2.0 $\pm$ 0.9 for 5 and 7 mCi, respectively). The starting time for stress SPECT acquisition (15 to 60 minutes), likewise, did not significantly affect image quality or liver overlap.

Overall, 34 of 39 patients with documented CAD (>75% on angiography) were found to have an ischemic pattern on the Myoview SPECT study (sensitivity = 87%). Sensitivity was also reported for each diseased vessel: 87% for the LAD, 83% for the LCx and 96% for the RCA. Sensitivities for detecting CAD are listed in the table below (derived from #5 in article).

TABLE #1: Sensitivity for Coronary Stenoses

	LAD	LCx	RCA	1-vessel disease	Multi-vessel disease
Ischemia	14/17 (82%)	11/13 (85%)	9/9 (100%)	15/17 (88%)	7/10 (70%)
Scar	12/13 (92%)	8/10 (80%)	15/16 (94%)	15/16 (94%)	8/10 (80%)
Overall	26/30 (87%)	19/23 (83%)	24/25 (96%)	30/33 (91%)	15/20 (75%)

The authors also correlated segmental wall motion on angiography with regional Myoview uptake. All segments with normal stress and rest perfusion on Myoview scintigrams were demonstrated to have normal wall motion on left ventriculography (148/148 segments). Abnormal wall motion was seen in 24/31 (77%) of segments with abnormal perfusion both at stress and rest. Stress-induced perfusion abnormalities were seen in 57 segments; 49 (86%)of these were associated with an angiographic wall-motion abnormality.

13) AUTHOR'S CONCLUSIONS: "It appears that even of Tc-99m tetrofosmin is used instead of the conventional Tl-201, dipyridamole-loading [stress] myocardial scintigraphy can be performed using a one-day method, and that this examination method has a diagnostic capability comparable to that of Tl-201."

14) REVIEWER'S COMMENTS:

A) Design strengths: The study has some strengths with respect to design and reporting of methodology and results, the most significant being a relatively large sample size of patients undergoing coronary angiograms as a truth standard. There was a detailed description of dosing, acquisition and processing procedures, and an emphasis on evaluating image quality. The study compared perfusion defects on Tc-99m tetrofosmin SPECT to angiographic wall motion abnormalities and coronary stenoses of $\geq$ 75%.

B) Design limitations: Though this study was one of the more significant literature trials provided by the sponsor in terms of sample size, several deficiencies remain which decrease its value as a supportive paper. It is not clear from the information submitted (English translation or sponsor's summary in the ISE) if this is a prospective trial or if medical records were reviewed retrospectively. No accounting was provided for the 52 patients who were enrolled but did not undergo coronary angiography.

There was no mention of methodology for "normalization" of tracer uptake. A consequence of this is that a segment-by-segment meta-analysis with other studies in the submission becomes difficult. Meta-analysis is made more difficult by the use of a different standard for significant CAD (75% stenosis) than in the other reports from the literature.

No mention was made if readers were blinded to patient history or angiographic results. This failure to take measures to minimize bias severely detracts from the supportive value of the study. Readers of the angiograms ideally should also be blinded to history and Myoview scan results, but no mention was made of this. Furthermore, an independent blinded read carries more weight than one done by consensus.

Specificity, PPV, NPV or accuracy was not reported for CAD patients as a whole or for each coronary artery.

C) Reviewer's conclusions:

Despite the failure to account for all 107 patients enrolled, the results show in 55 subjects good sensitivity for the technique for diagnosing CAD overall, and for the individual vessels. Sensitivity was good even for the LCx at 83%, far better than in the other literature trials submitted. The fact that a stenosis of $\geq$75% was considered significant may explain these better results, as such a stenosis is more likely to produce ischemia (and decreased perfusion on the Myoview study). Comparison of segmental Tc-99m tetrofosmin uptake with wall motion seen on angiography is of little value as normal motion may be seen in ischemic, but viable segments, especially at rest. Data supporting the choice of >45 minutes post-Myoview as an optimal scan time is weak, as well as the data supporting the use of a 7 mCi (259 mBq) dose for the stress images. Though the authors conclude the diagnostic capability of Myoview SPECT in the setting of pharmacologic stress to be comparable to that of Tl-201, there is no Tl-201 data to support this conclusion. The absence of blinded reader methodology unfortunately renders this study unable to support an efficacy claim for Myoview scintigraphy using dipyridamole as a substitute for exercise stress.

Clinical Review of Literature Study: Mahmood 1995 (pp. 1799-1802, vol. 7)

Study Title: "Combined Rest Thallium-201/Stress Technetium-99m tetrofosmin SPECT: Feasibility and Diagnostic Accuracy of a 90-Minute Protocol"
Authors: Mahmood, Gunning, Bomanji, Gupta, Costa, Jarritt, Swanton, Ell
Trial center: University College London Medical School
Reference: *Journal of Nuclear Medicine* 36, no. 6, 1995, pp. 932-935

1) STUDY OBJECTIVES: This study was conducted "to assess the feasibility and diagnostic accuracy of a combined protocol involving rest Tl-201 SPECT and stress imaging with Tc-99m tetrofosmin" (quote, p. 1799)

2) STUDY DESIGN: This study is a single-center, open-label, double-administration, (Tc-99m tetrofosmin, Tl-201) non-randomized prospective trial where 25 patients with known CAD underwent Tc-99m tetrofosmin stress imaging combined with Tl-201 scintigraphy at rest, in a 90-minute protocol. Results were compared to coronary angiography as a truth standard. Rest imaging was done first, using 74 mBq (3.0 mCi) of Tl-201. Subjects were then given a 6-minute infusion of adenosine, during which they would also exercise at 25-watts on a supine bicycle. At peak stress, 10 mCi of Tc-99m tetrofosmin was injected IV, followed by repeat SPECT imaging. Efficacy endpoints included sensitivity, specificity, diagnostic accuracy and predictive values of combined Tl-201/Tc-99m tetrofosmin SPECT for detecting stenoses of each of the 3 major vessels, as well as an overall diagnosis of CAD. There was no formal safety assessment except for vital signs, adverse events and ECG monitoring during stress testing.

3) STUDY TIMETABLE: A timetable was not provided for the overall study, but stress/rest injection/imaging protocols were schematized.

4) PATIENT POPULATION: 25 patients, male or female
   A) Inclusion criteria: Patients with known coronary artery disease, defined as ≥50% stenosis in at least one major vessel.
   B) Exclusion criteria: Obstructive airway disease, unstable angina, second- or third-degree AV block.

5) PRESTUDY PREPARATION: Patients were asked whenever possible to stop dipyridamole at least 72 hours, beta blockers at least 48 hours, and caffeine for 10 hours before testing. An I.V. cannula was inserted into the right arm, attached to a 3-way stopcock.

6) DOSAGE AND IMAGE ACQUISITION: The protocol called for a dose of 74 mBq (3.0 mCi) of Tl-201 to be given at rest and 370 mBq (10 mCi) of Tc-99m tetrofosmin (Myoview) during stress. SPECT of the myocardium was acquired using a GE dual-headed dedicated cardiac camera. Resting images were acquired beginning 20 minutes after the 3 mCi Tl-201 dose. Adenosine and bicycle stress would begin after the complete acquisition of the first set of images. The dose of adenosine was

to be 0.140 mg/kg/min I.V. at 1mg/ml normal saline over 6 minutes. Simultaneously, the patient would exercise supine on a bicycle ergometer for 6 minutes at low level (25 watts). The Myoview dose was given as a bolus at 4 minutes into the stress procedure. The second set of images would be obtained beginning 20 minutes after the completion of stress testing.

7) IMAGE PROCESSING AND INTERPRETATION: Following acquisition, images were processed using a Ramp filter and Hanning prefilter. The resulting transaxial images were used to obtain slices in the three cardiac axes. The slices were then divided into nine segments: two each for lateral, inferior, septal and anterior, as well as one for the apex. Visual inspection was used to determine if perfusion to a segment was normal or decreased; decreased segments was considered abnormal. Side-by-side rest and stress images were then interpreted to assess reversibility. Segments were assigned a coronary territory for subsequent correlation with angiography: anterior, septal and apical segments (5) to the LAD, lateral segments (2) to the LCx and inferior (2) to the RCA.

8) SAFETY EVALUATIONS were limited to recording of adverse events, pulse, systolic and diastolic blood pressure during pharmacologic and exercise stress. Vital signs were recorded at rest and every 2 minutes during the stress test, along with a continuous 3-lead ECG.

9) BLINDING AND METHODS TO MINIMIZE BIAS: Three investigators read the images and reached a consensus. There was no mention of blinding with respect to history or coronary angiography results.

10) EFFICACY ANALYSES AND STATISTICAL METHODS:
A) Safety data: Hemodynamic (BP and pulse) values were reported as mean ± standard deviation for rest and peak stress values.
B) Efficacy data: Sensitivity and specificity were reported for the scintigraphic images for each coronary territory, the LCx and RCA combined, and as a whole.

11) STUDY RESULTS
A) Demographics and Baseline Characteristics: 25 patients (23 men, 2 women, age range 36-73 years) with CAD were enrolled; no mention was made of withdrawals from the study. Thirteen had a previous MI, 3 had atypical chest pain, 22 had typical angina and 4 dyspnea. The mean and standard deviation for age was not given.
B) Safety Results: No mention was made of adverse events or administration of aminophylline or sublingual nitroglycerin. The means and standard deviations were given for heart rate and systolic BP at rest and peak stress: heart rate rose from 63.6 ± 9.8 to 90.3 ± 20.4 bpm. Systolic BP rose from 133.1 ± 17.4 to 144.1 ± 17.8 mmHg and diastolic BP from 82.6 + 10.1 at rest to 83.7 + 10.1 at peak stress.
C) Efficacy Results: The evaluation of efficacy in this study comprised a measure of sensitivity and specificity of adenosine/low level exercise Tl-201/Tc-99m

tetrofosmin SPECT for diagnosing CAD. Results were reported as a whole and for each major coronary artery by correlating myocardial segments with abnormal perfusion with angiographically stenosed arteries.

Overall, 20 of 25 patients with documented CAD were found to have an abnormal Myoview SPECT study (sensitivity = 80%). Sensitivity was also reported by segment: for the LAD territory, sensitivity was 85% (34/40); specificity was 70% (59/84); for the LCx, sensitivity was 69% (9/13); specificity was 70% (26/37); for the RCA, sensitivity was 78% (28/36); specificity was 71% (10/14). The above results are tabulated below.

TABLE #1: Diagnostic Results

STATISTIC	LAD	LCx	RCA	LCx + RCA	All vessels
Sensitivity	85% (34/40)	69% (9/13)	78% (28/36)	76% (37/49)	80% (71/89)
Specificity	70% (59/84)	70% (26/37)	71% (10/14)	70% (36/51)	70% (95/136)

12) AUTHOR'S CONCLUSIONS: "A combined myocardial imaging protocol involving Tl-201 scintigraphy at rest, followed by Tc-99m tetrofosmin imaging after stress, is a useful method to investigate the presence of CAD. The sensitivity and specificity in the detection of coronary artery stenosis, as shown on coronary angiography, are similar to that of tetrofosmin as a single agent, but they are less than thallium alone." (p. 1802, vol. 7)

13) REVIEWER'S COMMENTS:

A) Design strengths: The study has several strengths with respect to design and reporting of methodology and results. Patients were enrolled prospectively, and there was a detailed description of dosing, acquisition and processing procedures. The study compared Tl-201 rest/Tc-99m tetrofosmin stress SPECT to coronary angiograms as a truth standard. The authors analyzed results "by patient", and "by vessel", using 50% as the cutoff for stenosis severity.

B) Design limitations: Several deficiencies decrease this paper's value as supportive for the Myoview pharmacologic stress indication. The sample size was very small (25 patients). Inclusion and exclusion criteria were specified, but only briefly. No racial breakdown was given; only the age range was given. By including low-level bicycle stress with adenosine, the study is rendered unable to support a claim for Myoview using only pharmacologic stress. The criteria for image quality were not defined (as in Takaishi 1998). Segments were read only as normal or abnormal; there was no mention of criteria for decreased myocardial uptake of the tracer within a given segment, nor was there a methodology for "normalization" of tracer uptake. A consequence of this is that a segment-by-segment meta-analysis with other studies in the submission is now impossible. As in Takaishi 1998, the LAD was heavily weighted in the segment assignment: five of nine (2 anterior, 2 septal, 1 apical), and assumed always to include the apex.

The time period between angiography and the Myoview SPECT study was not given. No mention was made of readers being blinded to patient history or

angiographic results. Readers of the angiograms ideally should also be blinded to history and scintiscan results, but no mention was made of this. Furthermore, an independent blinded read carries more weight than one done by consensus..Accuracy, PPV and NPV were not reported for CAD patients as a whole or for each coronary artery. Furthermore, there was no formal statistical analysis of either efficacy or safety data (only sensitivity and specificity).

As for safety, adverse events were not mentioned for either Tl-201 or Myoview injection.

C) Reviewer's conclusions:

The results show a fairly acceptable sensitivity for the technique for diagnosing CAD overall, and for the LAD and RCA. As in Takaishi and Fukuzawa's papers, sensitivity was lowest for the LCx (69%).

The absence of blinded reader methodology, use of low-level bicycle exercise and use of Tl-201 as a rest imaging agent unfortunately render this study unable to support an efficacy claim for Myoview scintigraphy using adenosine as a substitute for exercise stress in the detection of CAD or myocardial ischemia.

APPEARS THIS WAY
ON ORIGINAL

Clinical Review of Literature Study: Takeishi 1998 (pp. 1803-1807, vol. 7)

Study Title: "Myocardial Tomography with Technetium-99m Tetrofosmin During Intravenous Infusion of Adenosine Triphosphate"
Authors: Takeishi, Takahashi, Fujiwara, Atsumi, Takahashi, Tomoike
Trial center: Yamagata University School of Medicine, Yamagata, Japan
Reference: *Journal of Nuclear Medicine* 39, no. 4, April 1998, pp. 582-586

1) STUDY OBJECTIVES: This study was conducted "to assess the feasibility and diagnostic value of 99m Tc-tetrofosmin tomography with ATP in patients with coronary artery disease and to examine the organ distribution of 99m tetrofosmin after intravenous ATP infusion" (quote, p. 1803)

2) STUDY DESIGN: This study is a single-center, open-label, double-administration, non-randomized prospective trial where Tc-99m tetrofosmin scintigraphy in the setting of pharmacologic stress with adenosine triphosphate (ATP) is compared to coronary angiography as a truth standard. Subjects enrolled consecutively were given a 5-minute infusion of ATP at 0.16 mg/kg/min. Three minutes into the ATP infusion, 10 mCi (370 mBq) of Tc-99m tetrofosmin was injected IV, followed one hour later by SPECT imaging. At the conclusion of stress imaging, subjects were given a second dose of Tc-99m tetrofosmin (20 mCi, 740 mBq). Rest SPECT was done 1 hour later. Efficacy endpoints included sensitivity and specificity of Tc-99m tetrofosmin SPECT for detecting patients with 1, 2 or 3 significant coronary stenoses (>50%), involvement of each of the 3 major vessels, and dynamic organ distribution of Tc-99m tetrofosmin during rest and ATP infusion. Safety assessment included vital signs, adverse events and ECG monitoring at baseline and during ATP infusion.

3) STUDY TIMETABLE: A timetable was not provided for the overall study, but stress/rest injection/imaging protocols were schematized.

4) PATIENT POPULATION: 65 consecutive patients with suspected CAD: 36 men, 29 women, mean age 67 (range not given).
   A) Inclusion criteria: Suspected coronary artery disease
   B) Exclusion criteria: Previous coronary angiography, angioplasty or CABG, or refused consent

5) PRESTUDY PREPARATION: All cardiovascular medicines were discontinued 24 hours before the test.

6) DOSAGE AND ADMINISTRATION: The protocol called for the dose of 370 mBq (10 mCi) of Myoview to be given at stress and 740 mBq (20 mCi) at rest. The dose of ATP was to be 0.16 mg/kg/min I.V. over five minutes.

7) IMAGE ACQUISITION AND INTERPRETATION: SPECT of the myocardium was acquired beginning one hour after the 10 mCi stress Myoview dose (15% window

at 140 KeV, 360 degree acquisition of 72 images, 64 x 64 matrix, of 40 seconds each). Following acquisition, images were processed using filtered back projection without attenuation correction. The resulting transaxial images were used to obtain slices in the three cardiac axes. The left ventricle was then divided into ten segments (2 each for the apex, anterior, lateral, inferior and septal regions) for visual interpretation. Visual inspection was used to determine if perfusion to a segment was decreased; a segment was scored from 4 = normal uptake to 0 = no uptake. Side-by-side rest and stress images were then interpreted to assess reversibility. Segments were assigned a coronary territory for subsequent correlation with angiography: anterior, septal and apical regions to the LAD, lateral region to the LCx, and inferior region to the RCA.

8) DYNAMIC ORGAN DISTRIBUTION: Though not central to supporting the efficacy of Myoview imaging with pharmacologic stress, an assessment was made of Tc-99m tetrofosmin organ distribution during rest and during ATP infusion. The purpose was to determine the optimal time for imaging after radiopharmaceutical injection. Ten patients underwent serial anterior planar rest and ATP stress imaging on separate days. Images were obtained at 15, 30, 45 and 60 minutes after the tracer was injected. Regions of interest were generated about the heart, left lung and liver, and the average counts per pixel determined. These values were normalized to the average count density in the heart at 15 minutes. For each timepoint, heart-to-lung and heart-to-liver ratios were computed from mean counts per pixel in the heart divided by those in the lung or liver, respectively.

9) CORRELATIVE IMAGING: Coronary angiography was done within 1 week after the Myoview study using the standard Judkins catheter. Significant stenoses were defined as 50% or greater.

10) SAFETY EVALUATIONS were limited to recording of adverse events, measurement of pulse and cuff blood pressure, and continuous ECG monitoring during the test.

11) BLINDING AND METHODS TO MINIMIZE BIAS: Two independent readers were blinded to patient history and angiographic findings. The final score of each segment was, however, reached by consensus. A single cardiologist, blinded to history and scintigraphic findings, was consulted to read the coronary angiograms.

12) EFFICACY ANALYSES AND STATISTICAL METHODS:

A) Safety data: Hemodynamic (systolic BP and pulse) values were reported as mean $\pm$ standard deviation for rest, post-dipyridamole and peak stress values.

B) Efficacy data: Descriptive statistics were reported for the relationship between scintigraphic and angiographic results, and reported as mean $\pm$ 1 standard deviation. The Bonferroni analysis of variance and the Student's T-test were employed, with a significance value of 0.05.

C) Organ distribution of Tc-99m tetrofosmin: The average organ activity for the liver, lungs and heart were plotted over time after injection of Tc-99m tetrofosmin, both for rest and ATP stress conditions.

13) STUDY RESULTS

A) Demographics and Baseline Characteristics:

Sixty-five consecutive patients with suspected CAD were enrolled consecutively. The mean age was 67 (range not given). Coronary angiography revealed 44 with CAD: 23 with 1-vessel, 12 with 2-vessel and 9 with 3-vessel disease, while 21 patients did not have significant stenoses. Of the 44 CAD patients, 11 had a previous myocardial infarction. Gender and racial breakdowns were not given.

B) Safety Results:

Overall, adenosine triphosphate infusion caused a rise in heart rate and fall in systolic and diastolic blood pressure. The mean heart rate rose from 68 $\pm$ 12 to 80 $\pm$ 13; systolic BP from 142 $\pm$ 19 to 126 $\pm$ 24, and diastolic BP from 81 $\pm$ 13 to 71 $\pm$ 15. All symptoms disappeared by 1 to 2 minutes post injection. Chest pain was the commonest AE, experienced by 19 patients (29%), and ischemic ST changes were seen in 17 (26%) of the subjects. Transient PR interval prolongation was seen in two patients (3%), and second-degree AV block in two others (3%). No patient needed intravenous aminophylline to counteract the effects of ATP. Adverse events during or after ATP infusion are listed in Table #1 below.

TABLE #1: Adverse Events

Adverse event	n (%)	Adverse event	n (%)
Chest pain	19 (29%)	Dyspnea	1 (2%)
Headache	8 (12%)	ST-depression > 1mm.	17 (6%)
Nausea	4 (6%)	First-degree AV block	2 (3%)
Flushing	3 (5%)	Second-degree AV block	2 (3%)
Abdominal discomfort	2 (3%)		

C) Organ Distribution Results:

For resting Tc-99m tetrofosmin images, the heart-to-liver and heart-to-lung ratios were maximal at the 60-minute timepoint: 1.43 $\pm$ 0.92 and 3.71 $\pm$ 0.89, respectively. For ATP stress images, the ratios at 60 minutes were 1.32 $\pm$ 0.36 for heart/lung and 3.43 $\pm$ 0.85 for heart/liver.

D) Efficacy Results:

The evaluation of efficacy in this study comprised a measure of sensitivity and specificity of Tc-99m tetrofosmin scintigraphy against coronary angiography for overall diagnosis of CAD, and specific measures of sensitivity for patients with disease involving each coronary vessel. These are summarized in Table #2 on the next page.

TABLE #2: Comparison of Tc-99m Tetrofosmin SPECT with Angiography

STATISTIC	All pts.	Non-MI pts.	LAD	LCx	RCA
Sensitivity	39/44 (89%)	28/33 (85%)	27/34 (79%)	10/16 (63%)	20/24 (83%)
Specificity	17/21 (81%)				

14) AUTHOR'S CONCLUSIONS: Results "indicate that Tc-99m tetrofosmin offers favorable tracer biodistribution after intravenous ATP infusion. Tc-99m tetrofosmin tomography with ATP is a practical method for the noninvasive diagnosis of coronary artery disease" (p. 1807). The author also concludes that the 60-minute timepoint for imaging after Myoview injection offers an optimal compromise for a one-day protocol, given the higher heart-to-organ ratios and time for tracer to decay after the first injection, but a total time for imaging short enough for adequate patient throughput.

15) REVIEWER'S COMMENTS:

A) Design strengths: The study has a number of strong points with respect to design and methodology. The trial was prospective and patients were enrolled consecutively, reducing the potential for selection bias. Inclusion and exclusion criteria were specified. There was a detailed description of dosing, image acquisition and processing, and calculation of tracer uptake in heart, lung and liver. Blinded readers were employed to interpret both the SPECT and coronary angiograms, which were used as a truth standard. The criterion for significant stenoses was clearly specified at ≥50%. Unlike in the paper by Fukuzawa et. al, the segmental division of the LV was well defined (though not illustrated). The scoring system for segmental uptake of the tracer was also well defined.

B) Design limitations: Along with Fukuzawa 1996, this trial was one of the more robust studies from the literature chosen by the sponsor to support an efficacy claim for Myoview with pharmacologic stress. Unfortunately, adenosine triphosphate is not yet approved by FDA, and cannot be included in the revised labeling sought by the sponsor. Aside from this, the study has other limitations which decrease its supportive value:

- Age range and gender/racial breakdown not given.
- Adverse events not recorded after rest Myoview injection.
- Specificity given only for group as a whole, not individual vessels.
- No "by-segment" or "by vessel" analysis of efficacy, only "by patient".
- Consensus read of segmental scores by blinded readers.
- Too-heavy weighting of segments to LAD: 6 of 10 including both apical.
- No report of PPV, NPV or specificity for individual vessels.
- No mention of image quality (though implied in organ uptake ratios).
- Not clear if the 10 organ distribution patients were separate from the 65 patients with suspected CAD studied for efficacy.

C) Reviewer's conclusions: This study cannot be used to support a pharmacologic stress indication for Myoview as adenosine triphosphate has not been approved by FDA for diagnostic use. The results show Myoview imaging with ATP stress to have an adequate level of sensitivity for detecting CAD overall, and for each vessel. The current authors reported a sensitivity of 63% for the LCx, which, though not optimal, is better than the Fukuzawa 1996 result of 47%. The sample size of 65 patients makes this, along with Fukuzawa 1996 the most robust study among literature trials supporting efficacy in this NDA supplement submission. With respect to safety, adverse events and vital sign changes were transient (1-2 minutes), and did not require aminophylline administration. Comparison of AE's and vital sign changes after ATP and after the rest injection of Myoview would help exclude Myoview as a cause for these changes.

Clinical Review of Literature Study: Thorley 1995 (pp. 1808-1814, vol. 7)

Study Title: "Evaluation of Tc-99m-Tetrofosmin as a Myocardial Perfusion Agent in Routine Clinical Use"
Authors: Thorley, Ball, Sheard, Sivananthan
Trial center: Radionuclide Dept., Killingbeck Hospital, Leeds, S146UQ, England
Reference: *Nuclear Medicine Communications* 1995, no. 16, pp. 733-740

1) STUDY OBJECTIVES: This study was conducted "to assess the diagnostic accuracy SPECT imaging with Tc-99m tetrofosmin comparing exercise (treadmill) stress and pharmacologic stress with I.V. dobutamine" (quote from sponsor in ISE, p. 1680, vol. 7 of submission).

2) STUDY DESIGN: This study is a single-center, open-label, triple-administration, non-randomized prospective trial where exercise and pharmacologic (dobutamine) stress Tc-99m tetrofosmin scintigraphy are compared, with coronary angiography as a truth standard. All subjects underwent on separate days two injections of 10.8 mCi (400 mBq) Tc-99m tetrofosmin (Myoview): at rest and during a 6-minute dobutamine infusion or treadmill exercise. Safety assessments were not reported. Efficacy endpoints included agreement in the results of segmental uptake of Tc-99m tetrofosmin among the 3 scans, and sensitivity, specificity and accuracy of the three Myoview studies for stenoses of each major vessel and CAD as a whole.

3) STUDY TIMETABLE: A timetable was not provided for the study, and stress/rest injection/imaging protocols were not schematized.

4) PATIENT POPULATION: 297 consecutive patients with known or suspected CAD
   A) Inclusion criteria: Suspected CAD
   B) Exclusion criteria: None specified

5) PRESTUDY PREPARATION: Patients were asked whenever possible to stop beta-blockers and calcium antagonist medications at least 48 hours before testing. Food was discontinued 4 hours before Myoview injection. After Myoview injection, patients were given buttered toast to facilitate hepatobiliary clearance of Tc-99m tetrofosmin prior to scanning.

6) DOBUTAMINE STRESS PROTOCOL AND MYOVIEW DOSAGE: The protocol called for a dose of 400 mBq (10.8 mCi) of Myoview to be given at rest and stress sessions, on separate days (with the exception of 2 patients, who underwent same-day imaging with 250 MBq at stress followed by 759 mBq at rest four hours later). For pharmacologic stress, the dose of dobutamine was to be administered in steps: 5, 10, 25, 30, 35 and 40 ug/kg/min I.V. at 4 minutes for each step. Myoview would be given as an IV bolus at 2 minutes into the last stage of dobutamine infusion (40 ug/kg/min.), then the infusion continued for 2 more minutes. If there was no significant rise in the pressure-rate product at the maximum dobutamine dosage, 0.3 mg. of atropine was to be given as an I.V. bolus

and Myoview given 1 minute later. A repeat 0.3 mg. atropine dose was to be given if necessary. If the patient developed chest pain, >20 mmHg drop in systolic blood pressure or ischemic (ST-depression) changes on the ECG, the dobutamine infusion was to be stopped and Myoview given.

7) EXERCISE STRESS PROTOCOL: Exercise stress was carried out on a treadmill, according to the standardized Bruce protocol, with 400 mBq (10.8 mCi) of Myoview injected 1 minute prior to completing exercise. Criteria for termination of exercise included achievement of the age-predicted maximal heart rate, severe angina, significant (>2mm) ST depressions, physical exhaustion, exertional hypotension or dyspnea limiting exercise.

8) IMAGE ACQUISITION AND INTERPRETATION: SPECT of the myocardium was acquired in the supine position beginning 45 minutes after the stress Myoview dose and 1 hour after a resting dose. (20% window at 140 KeV). A Siemens Orbiter rotating gamma camera fitted with a LEAP collimator acquired sixty-four 128 x 128 pixel images of 15 sec. each for 180° from RAO to LPO positions. Following acquisition, images were processed using a Butterworth prefilter and back projected using a ramp filter. No attenuation correction was used. The resulting transaxial images (zoomed to 64x64pixels) were used to obtain slices in the three cardiac axes. The myocardium was then divided into 17 segments (four short-axis cuts with 4 segments each, and one apical segment on the vertical and horizontal long-axis cuts); and a quantitative polar map (bulls-eye plot) constructed. Segments were then assigned a coronary territory for correlation with contrast angiography. For the purpose of this assessment, the anterior wall corresponds to the LAD; lateral to the LCx, inferior to the RCA, and septal or apical to LAD or RCA, depending on other defects present. Uptake in each segment was normalized to the segment with the maximum counts on the stress image, and expressed as a percentage. Segments with >80% activity in the inferior wall and >85% in the other three walls were considered normal. Defects were considered significant if involving $\geq$ 2 adjacent segments in the same slice or the same wall in $\geq$ 2 adjacent slices. Side-by-side rest and stress images were then interpreted to assess reversibility.

9) SAFETY EVALUATIONS were not reported in the article.

10) BLINDING AND METHODS TO MINIMIZE BIAS: Two investigators read the scintigraphic images and arrived at a consensus. No mention was made of blinding with respect to history or coronary angiography results.

11) CORRELATIVE IMAGING: Coronary angiography was done before Myoview scintigraphy (time frame not indicated). Lesions were grouped into categories of 50-70%, 70-99% and 100% narrowing when compared to a normal segment of the same vessel. Proximal stenoses of >50% and distal ones of >70% were considered significant. Angiograms were interpreted by two independent observers; no mention was made of blinding.

12) STATISTICAL METHODS:

Descriptive statistics by-patient and by-vessel were reported for the relationship between scintigraphic and angiographic findings (sensitivity, specificity). PPV. NPV and accuracy were not reported.

13) STUDY RESULTS

A) Demographics, Baseline Characteristics and Adverse Events

297 patients with suspected or known CAD were enrolled (204 men and 93 women); no mention was made of withdrawals from the study. The patients' mean age was 57 ± 10 years, range 26 to 79. Nearly all had angina or similar pain. 187 underwent exercise treadmill testing and 105 dobutamine stress because of inability to exercise on a treadmill. Of the 86 patients for whom coronary angiography data is available, 63 had exercise stress and 23 underwent dobutamine stress. Seventy of the 86 patients had significant CAD (>50% stenoses); 30 had one-vessel, 26 two-vessel and 14 three-vessel disease. Ten had normal coronaries; 6 had small-vessel disease or stenoses <50%. Two of the 297 patients experienced nausea and vomiting lasting approx. 1 hour, followed by a metallic taste sensation 12 hours after tracer injection. There were no other reported adverse events.

B) Efficacy Results

The evaluation of efficacy in this study comprised a measure of sensitivity and specificity of Tc-99m tetrofosmin SPECT for diagnosing CAD, under exercise and dobutamine pharmacologic stress conditions.

Overall, 63 of 70 patients with angiographically documented CAD were found to have an abnormal Myoview SPECT study (overall sensitivity = 90%), while 7 of 10 with normal coronaries had an normal Myoview SPECT scan (specificity = 70%). The overall sensitivity of Myoview studies in patients undergoing exercise stress was 55/63 (88%) and dobutamine stress 22/23 (95%). Sensitivity and specificity for detection of individual stenoses was also reported for both forms of stress (Tables #1 and 2). The difference in sensitivities for detecting stenoses were greatest for the LAD (78% for exercise vs. 50% for dobutamine) and LCx (87% for exercise vs 60% for dobutamine) territories. For specificity, the LAD was 90% for exercise and 75% for dobutamine.

TABLE #1: CAD Detection: Exercise Stress (n = 63 patients, 189 territories)

STATISTIC	LAD	LCx	RCA	All vessels
Sensitivity	29/37 (78%)	13/15 (87%)	27/30 (90%)	69/82 (84%)
Specificity	19/21 (90%)	38/40 (95%)	20/28 (71%)	77/89 (87%)

TABLE #2: CAD Detection: Dobutamine Stress (n =23 patients, 69 territories)

STATISTIC	LAD	LCx	RCA	All vessels
Sensitivity	7/14 (50%)	3/5 (60%)	15/17 (88%)	25/36 (69%)
Specificity	6/8 (75%)	14/16 (88%)	4/5 (80%)	24/29 (83%)

14) AUTHOR'S CONCLUSIONS: "Tc-99m tetrofosmin is a highly sensitive and specific agent for the detection of coronary artery disease, using both exercise and dobutamine stress, with few limitations." (quote, p. 733 of article, p. 1808, vol. 7 of submission)

15) REVIEWER'S COMMENTS:

A) Design strengths: The study has several strengths with respect to design and reporting of methodology and results. This paper was the only study to compare exercise and dobutamine Myoview SPECT images, and compare them to coronary angiograms as a truth standard. The sample size at first glance is large (86 patients) compared to others in the submission, both from the sponsor and the literature. Patients were enrolled prospectively and consecutively; and there was a detailed description of dosing, acquisition and processing procedures. Criteria for abnormal SPECT images were explained in great detail and substantiated from the literature. Evaluation of efficacy was made on a patient-by-patient as well as a segment-by-segment basis.

B) Design limitations: Several deficiencies in the paper should be mentioned. Only 23 patients underwent both correlative angiography and dobutamine stress Myoview SPECT; these comprise the most important subset for analysis in this report. It is unfortunate that exercise and pharmacologic stress were done on different groups of patients. In addition, dobutamine is not as yet approved by FDA, and cannot be used in revised labeling sought by the sponsor. Inclusion and exclusion criteria were not specified.

Criteria for evaluating image quality were not defined. No mention was made if the Myoview SPECT readers were blinded to patient history or angiographic results. Readers of the angiograms ideally should also be blinded to history and Myoview scan results, but no mention was made of this. Also, a consensus read does not carry the weight of an independent blinded read. The time between angiography and Myoview SPECT was also not reported.

PPV, NPV and accuracy were not reported for CAD patients as a whole, for each segment or for each coronary artery.

C) Reviewer's conclusions: This study cannot be used to support a pharmacologic stress indication for Myoview as dobutamine has not been approved by FDA for diagnostic use. This problem aside, the results here do little to support efficacy claims for dobutamine/Myoview due to the small sample size (23). Had exercise and dobutamine been compared *in the same patient group*, and readers of scans be blinded to clinical/angiographic findings, the study might carry more weight. Overall results indicate comparable and acceptable sensitivity and specificity for both exercise and dobutamine Myoview SPECT in diagnosing and localizing CAD, but exercise was somewhat better than dobutamine in the LAD distribution (78% vs. 50% sensitivity, 90% vs. 75% specificity).