TABLE #6: ADVERSE EVENTS RELATED TO DIPYRIDAMOLE INJECTION
(modified from p. 406, volume 3 of submission)

Body System	Event	(n=64)
Body as a Whole	Headache	17 (27%)
	Flushing	10 (16%)
Nervous	Dizziness	4 (6%)
	Lightheadedness	2 (3%)
Cardiovascular	Chest pain	25 (39%)
	Arrhythmia	2 (3%)
Respiratory	Dyspnea	4 (6%)
Digestive	Nausea	5 (8%)
	Abdominal cramps	2 (3%)

Reviewer's comment: It is unclear from the submission what distinguishes an AE associated with dipyridamole from one included in the "general" AE list of Table #5. Furthermore, the Philadelphia center is included here, so at least we know that some of the data was captured on the CRF's. It is unfortunate that the original protocol called for stress imaging first, as it is impossible to completely differentiate AE's possibly related to dipyridamole plus Myoview from those related to Myoview alone. This is further hampered by the lack of data pertaining to time between the AE and Myoview administration.

2) Vital Signs:

Changes from baseline to peak stress values were statistically significant for mean maximum systolic blood pressure (BP) and pulse, but not diastolic pressure. Mean maximum diastolic BP showed a slight decrease from baseline values. Vital sign changes outside a specified range (>15 bpm for heart rate, >20 mm Hg for BP) were also noted: 1/64 (1.6%) had a decrease in HR of >15 bpm, while 29/64 (45%) experienced an increase of >15 bpm. For systolic BP, 4/64 (6.3%) and 6/64 (14%) had decreases and increases of >20 mm Hg, respectively. For diastolic BP, 2/64 (3.1%) and 0/64 (0%) %) had decreases and increases of >20 mm Hg, respectively. Data pertaining to timing of vital sign measurements with respect to Myoview administration was not given. Scatterplots were submitted in the Safety Response received from the sponsor 7/26/99, and indicated no major concerns.

TABLE 7: VITAL SIGNS (From p. 407 of submission).

Parameter	Heart rate	Systolic BP	Diastolic BP
Baseline	69.9 (12.7)	137.3 (27.7)	78.8 (11.4)
Maximum	84.5 (14.5)	140.8 (28.2)	76.4 (11.5)
Difference	14.5 (11.6)	3.5 (18.1)	-2.4 (9.3)
Range			
P-values	0.0001	0.1310	ND

3) ECG's:

S-T segment changes for the 63 subjects studied (data missing from 1); were the only parameter analyzed. ST changes >1mm were considered ischemia. Four of 63 (6%) had depressions >1mm; one (2%) of >2.5 mm.

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

F) Efficacy Results

The evaluation of efficacy in this study addressed endpoints of sensitivity, specificity and predictive values for Myoview SPECT when compared to coronary angiography as a standard of truth, overall and for the individual vessels, in 58 subjects. Five patients either did not undergo angiography or did not have films available for blinded interpretation. A sixth subject had a suboptimal Myoview study, judged as uninterpretable. Agreement between angiography and the Myoview scans was evaluated on a subject-by-subject and vessel-by-vessel basis, and presented as the Kappa statistic and its 95% confidence interval. To qualify as abnormal, a stenosis must be ≥ 50% on the angiogram. Abnormal Myoview SPECT studies must be graded as 1, 2, 3 or 4 (slightly reduced to absent tracer uptake) on rest and/or stress images.

TABLE 8: DIAGNOSTIC EFFICACY

STATISTIC	Overall	LAD	LCx	RCA
Sensitivity	95.6%	71.0%	40.0%	96.2%
Specificity	30.8%	44.4%	78.8%	25.0%
Positive predictive value	82.7%	59.5%	58.8%	51.0%
Negative predictive value	66.7%	57.1%	63.4%	88.9%
Agreement	81%	59%	62%	57%
Kappa	0.33	0.16	0.20	0.20
95% confidence int.	-0.03 - 0.68	-0.10 - 0.41	-0.07 - 0.46	-0.04 - 0.43

Of the 21 patients with single vessel disease, 19 had abnormal Myoview scans (90.5%); 100% of the 11 patients with 2-vessel and 13 patients with 3-vessel disease had abnormal Myoview tomograms. In the population of 59 patients undergoing coronary angiography, 177 arteries were evaluated. Due to the single unreadable Myoview image (see above), the vessel data from one subject (3 vessels) was excluded from the analysis. For the remaining coronary arteries, the overall sensitivity was 69.5% (57/82) and specificity 50.0% (46/92). For the purpose of this analysis, the apex was considered to represent territory perfused by both the RCA and LAD, if no other perfusion abnormalities were seen. This resulted in false-positive results for 4 patients overall (two patients in each vessel distribution).

Bowel and liver activity have the ability to complicate interpretation of the Myoview images, particularly of the inferior wall. Uptake in these two organs was graded as absent, mild, moderate or severe. Of the 64 subjects, 23 (36%)

had no liver activity at stress; 41 (64%) had mild to severe activity at stress; 33 (52%) had no liver activity at rest and 31 (48%) had mild to severe hepatic uptake at rest.

For the bowel, 42/64 (66%) had no activity at stress; 22/64 (33%) had mild to severe activity at stress. For rest, 53/64 (83%) had no bowel activity and 11/64 (17%) had mild to severe activity.

Dilatation of the left ventricle due to infarction, cardiomyopathy or LV failure, was seen on stress images of 24/62 patients (39%) and rest images of 15/62 patients (24%).

Overall quality of the Myoview SPECT images was rated subjectively on a scale of 1 (poor) to 10 (excellent), by a consensus of 3 blinded readers. In addition, an "overall interpretation" score was determined according to the same 10-point scale. According to the sponsor, 55/64 (86%) achieved a quality score of 6 (good) or better; 56/63 achieved an "overall interpretation" score of 6 or better. Correlation of liver or bowel uptake with these scores indicated, to the sponsor, a negative correlation between bowel uptake and the two scores, but not liver uptake.

Reviewer's comment: The sponsor has not explained the differences between "overall interpretation" and "quality evaluation" scores, nor has the sponsor defined the objective image criteria for assigning a scan a given value. Also, a consensus read is not as credible as independent reads, even if blinded.

12) SPONSOR'S CONCLUSIONS (p. 411, vol. 3 of submission)

- "Tc-99m tetrofosmin myocardial perfusion imaging with IV dipyridamole pharmacologic stress testing showed high sensitivity (95.6%) for detection of CAD in this subject population, which had a 78% CAD prevalence. The specificity (30.8%) for the detection of CAD was lower than the sensitivity, reflecting both a pre-test selection bias and a post-test referral bias, and the protocol-specified low threshold for assessing a scan as abnormal. The overall sensitivity for detection of multi-vessel disease was 100%".

- "Tc-99m tetrofosmin myocardial perfusion imaging with intravenous dipyridamole pharmacologic stress testing had an overall sensitivity and specificity of 69.5% and 50.0%, respectively, for localization of CAD to individual vessels. In general, the majority of vascular territories showed perfusion results that agreed with coronary angiography findings. The lowest sensitivity for CAD was seen in the LCx, which is consistent with the literature. Lower sensitivity for specific vessels is expected in subjects with multi-vessel disease, given the relative- but not absolute-perfusion pattern obtained with gamma emitting radiopharmaceuticals. Technically good or excellent images were obtained in the majority of subjects".

- "There were no serious or significant adverse events or vital sign abnormalities noted with Tc-99m tetrofosmin use in this study.

[In conclusion] "Intravenous administration of Tc-99m tetrofosmin at a total dose of 32 mCi is safe and efficacious for stress/rest myocardial perfusion imaging when used with IV dipyridamole pharmacologic stress testing".

13) REVIEWER'S COMMENTS

A) Trial design and protocol execution:

The design of this trial, a multi-center, open-label, non-randomized type, is appropriate for this Phase 3 investigation. The protocol was followed closely in all centers, though a few minor deviations occurred (mostly in the dose of Myoview given). There were no subject dropouts, however, both efficacy and safety data was missing from a number of subjects. The sample size is small to begin with. The study utilized blinded interpretation of images for primary efficacy assessment, though final interpretation was by consensus of the three blinded readers rather than independent reads. The provision of a study timetable would have made it easier to follow the overall study design. Ideally, the use of a similar Tc-99m perfusion agent (i.e. Cardiolite) as a comparator to Myoview would be desirable.

B) Safety, toxicity 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, much could be done to improve the quality of the safety database. A number of specific questions raised during review of this study report need to be answered:

1) It is not clear how long or how frequently patients were to be followed for adverse events after injection of Myoview.
2) It is unfortunate that the original protocol called for stress imaging first, as it is impossible to completely differentiate AE's, vital signs and ECG changes related to dipyridamole plus Myoview from those related to Myoview alone. Such an analysis would be further hampered by the lack of data pertaining to time between the AE or vital sign/ECG measurement and study drug administration.
3) The sponsor notes that no AE's were reported at the Philadelphia center (26 patients); this was most likely due to reporting error, which would render AE data for this study incomplete. The sponsor lists percentages in the table below with 64 as the denominator; perhaps it would be more appropriate to use 38, the number of patients at the other two centers, as the denominator.
4) Substantially more adverse events were considered related to dipyridamole infusion than are listed in Table #5. It is unclear from the submission what distinguishes an AE associated with dipyridamole from one included in the "general" AE list of Table #4. Furthermore, the Philadelphia center is included here, so at least we know that some of the data was captured on the CRF's.

5) The QT and QTc intervals, an important measure of drug toxicity, were not reported in the tables.
6) Shift tables of safety data would be very helpful.

C) Efficacy results:

1) The kappa statistics for agreement between coronary angiography and Myoview SPECT (0.33 for subject-based agreement, 0.16, 0.20 and 0.20 for LAD, LCx and RCA vessel-based agreement, respectively) are poor, even according to the sponsor.
2) The sponsor has not explained the differences between "overall interpretation" and "quality evaluation" scores, nor has the sponsor defined the objective image criteria for assigning a scan a given value.
3) A consensus interpretation of SPECT images is not as credible as independent reads, even if performed by blinded readers.
4) With a small sample size to begin with, the missing coronary angiography data from five of 64 patients becomes significant.
5) The specificity of Myoview was poor, most likely due to a bias toward selecting patients with CAD (78% prevalence in subject population).
6) Sensitivity for disease in the LCx vessel was also low (40%). Though the sponsor indicates this to be consistent with reports in the literature, this raises concerns when one considers Myoview SPECT as a screening test for CAD in the setting of pharmacologic stress.
7) The absence of a blinded reader's assessment of image quality raises the possibility of bias in the sponsor's conclusion that Myoview scans were "technically good to excellent in the majority of subjects" (p. 411). "Image quality" is testimonial and not crucial to the claim.

D) Reviewer's conclusions:

This study does suggest that dipyridamole/Myoview studies may be useful in the evaluation of suspected CAD, however, the sample size is small (further compromised by missing angiographic data). A major drawback in the study design is the use of consensus rather than independent interpretation of images by the blinded readers.

Perhaps the most important addition to the safety assessment would be an evaluation of adverse events after the rest injection of Myoview, and comparison with AE's experienced following the post-dipyridamole stress Myoview injection. Shift tables were not submitted in the supplement or the Response to FDA Comments (Vol. 10, received on 7/26/99). Though the drug has an acceptable safety record thus far in the setting of exercise stress, and the likelihood is that adverse events reported in this supplement are due to the stress agents and not Myoview, such a study would provide a definitive answer to this question.

8:4:2 Study #PR95-302 (Study Report #2955) Volume 5, pp. 1103-1344

Study Title: "Comparison of Dipyridamole-201-Thallium with Dipyridamole-Technetium-99m Tetrofosmin SPECT Imaging in Patients with Angiographically Confirmed Coronary Artery Disease". This study is one of two trials conducted by the sponsor intended to support the efficacy of Myoview in the setting of dipyridamole stress.

1) STUDY OBJECTIVE: (quoted from sponsor) This Phase 3 study was conducted "to compare sensitivity and accuracy of dipyridamole-thallium-201 SPECT and technetium-99m tetrofosmin/dipyridamole SPECT for detection of severity and extent of coronary artery disease (CAD)".

2) STUDY DESIGN: GENERAL

This study was of the open-label, two-center double-administration, crossover type, without placebo. Tc-99m tetrofosmin (Myoview) SPECT myocardial perfusion images obtained at rest and after dipyridamole infusion were compared to dipyridamole/thallium-201 studies performed within 2 weeks of the Myoview study. The first 5 patients underwent Tl-201 first; the remainder, Myoview first. Scintigrams were interpreted by two blinded readers who reached a consensus, and compared to coronary angiograms as a truth standard. Coronary angiograms were to be performed before the SPECT studies; only patients with documented CAD were admitted to the study. Safety was assessed through monitoring of adverse events, vital signs and ECG's.

Reviewer's comment: The enrollment procedure was sequential, and does not represent true randomization.

3) PATIENT POPULATION

The original protocol #PR95-302 called for enrollment of 25 patients in one institution; 26 patients from two centers actually enrolled. The patients' age range was to be 18-80 years. The protocol called for entry of patients meeting inclusion/exclusion criteria, with angiographically documented CAD. Patients were enrolled from 2 groups: Group 1 had a significant (≥50%) stenosis of at least 1 epicardial coronary artery on angio, while Group 2 had inducible ischemia as demonstrated by dipyridamole/Tl-201 SPECT in addition to angiographically proven CAD.

Reviewer's comment: The first pivotal trial, #P53-006, enlisted patients with documented or suspected CAD, one of several design differences making the pooling of data with this trial more difficult.

4) PRESTUDY EVALUATION

The protocol called for a pre-study evaluation including clinical diagnosis, review of cardiac catheterization findings, gender, birth date and race. The above were to be recorded in the Case Report Form and informed consent signed. Vital signs were to be conducted prior to enrollment.

5) INCLUSION AND EXCLUSION CRITERIA

A) Inclusion criteria

1) Adult patients 18-80 years of age.
2) Subjects must have angiographically documented CAD, with at least 1 epicardial vessel ≥50% stenosis.
3) Positive dipyridamole/Tl-201 scan within 10 days of catheterization.
4) Males or non-pregnant, non-lactating females.

B) Exclusion criteria

1) Patients treated for bronchospasm or taking theophylline compounds.
2) Unstable angina within 48 hours of testing.
3) Patients with hemodynamic instability.
4) Subjects with left bundle branch block.
5) Patients who are unwilling or unable to sign informed consent without an available proxy.
6) *Patients with second-degree or third-degree AV block.
7) *Severe valvular heart disease.
8) *Uncontrolled arrhythmia.
9) *Use of short-acting nitrates within 1 hour before injecting drug.
10) *Use of dipyridamole or theophylline up to 48 hours before injection.
11) *Consumption of caffeine within 8 hours before injection.
12) *Significant vascular event or intervention between invasive and non-invasive studies.
13) *Patient unwilling or unable to comply with protocol.

*Reviewer's comment: * Several of the exclusion criteria in the original protocol were deleted in an amendment of 11/8/95 and the study report on page 1116. The deletions were listed on page 1126.*

6) STUDY DESIGN: TIMETABLE

TABLE #9: (from page 1202, vol. 5 of submission)

SCHEDULE OF ASSESSMENTS

	Pre-Enrollment	Rest	Pre-Stress	Post-Stress
Cath.Report	X			
Pulse			X	X
Blood Pressure			X	X
Side-effects				X
Imaging		X		X

Reviewer's comment: The absence of safety assessments after the resting study makes it impossible to separate AE's and vital sign changes due to Myoview from those due to the stress agent dipyridamole. This constitutes a design flaw from a safety perspective.

7) DOSAGES AND ADMINISTRATION:

Dipyridamole was to be given as an IV infusion at 0.56 mg/kg for 4 minutes (0.14 mg/kg/min) prior to the first dose of Myoview. The maximum dose was to be 60 mg. per patient.

Myoview was to be given as two bolus doses, 5-8 mCi (185-296 mBq) for rest imaging, and 25-35 mCi (925-1295 mBq) for stress imaging three minutes after completion of the dipyridamole infusion which was started 1 to 4 hours after the completion of the rest images. The total dose was not to exceed 43 mCi. The subject, drug administrator, safety monitors and staff were not blinded with respect to the study drug given (open-label).

Thallium-201 was to be given as a 3 mCi dose three minutes after completing the infusion of dipyridamole. Imaging was to be done 5-10 minutes later for stress and 3-4 hours later for rest.

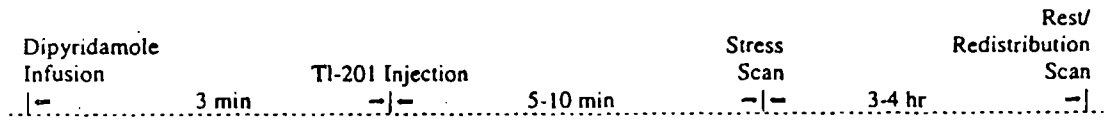
Aminophylline (100-125 mg. iv) was to be given according to each study center's routine protocol, if needed to reverse dipyridamole-induced symptoms. Each such administration was to be recorded in the CRF.

Imaging protocols for both thallium-201 and Tc-99m tetrofosmin are portrayed in Fig #1 below. The two tests were to be within 2 weeks apart. Times are after start of dipyridamole infusion (p 1115, vol. 5 of submission).

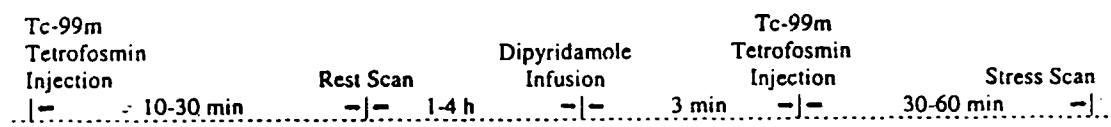
Figure 1

Time Scale for Stress Protocols

Thallium-201 Imaging



Technetium-99m Tetrofosmin Imaging



8) SPECT IMAGE ACQUISITION: SPECT mages were to be acquired 5 to 10 minutes after Tl-201 injection for stress and 3-4 hours later for rest. For Myoview, imaging was started 10-30 minutes after the rest injection, and 30-60 minutes after the stress injection. Acquisition parameters were described in detail in the protocol.

9) IMAGE INTERPRETATION: Reconstruction was to be done in short axis and horizontal/vertical long axes, using the same filter (not specified) for both Tl-201 and Myoview. The left ventricle was divided into 13 segments (apex and 3 slices to base each with 4 segments: anterior, lateral, inferior, septal). The apex was judged on the mid-vertical long-axis slice. Tracer activity was scored from 0 =

normal to 4 = absent uptake. Defects were assigned to the individual vessels as follows: anterior or septal: LAD; lateral: LCx; inferior: RCA. Solitary apical defects were not assigned to any artery, however, apical defects adjacent to other defects were assigned to the respective vessel.

Reviewer's comment: In the Study Report, the myocardium was divided into 14 segments for analysis; in the CRF, only 13. Two apical segments were studied in the final report.

10) BLINDING AND METHODS TO REDUCE BIAS: Each investigator was to supply the Core Laboratory with a disk containing the images, to be processed into a common format for the blinded readers. The rest and stress images were displayed and assessed side-by-side for a paired consensus read by 3 readers, blinded to image origin and patient diagnosis.

Reviewer's comment: A consensus interpretation of SPECT scans is not as credible as independent reads, even if performed by blinded readers.

11) CORRELATIVE IMAGING: Coronary angiography was to be performed within 2 weeks prior to the Myoview study, recorded and results compared with the diagnoses obtained in this study. Interpretation was to be by one angiographer. Since a positive diagnosis is an entry criterion, blinded reading of the angiogram was not carried out. Angio results were recorded as to date of procedure, % area and diameter stenosis of each vessel (LAD, LCx, RCA, LM), as obtained through computerized processing. Vessels with >50% diameter stenosis were considered abnormal. Stenosis severity was recorded for each lesion as <50%, 50-74%, 75-89%, 90-99% and 100%.

12) SAFETY EVALUATIONS

A) Pre-study baseline:

Subjects were to be given a complete history and physical examination with vital signs (pulse and blood pressure) and ECG. Informed consent was to be obtained, inclusion and exclusion criteria checked, and these procedures to be performed during the two days prior to study participation.

B) Post-procedure:

1) Adverse Events: Monitoring for AE's was to be carried out beginning at the time of dipyridamole stress. To be recorded were date of onset, serious vs. nonserious, and possibility of relationship to Myoview administration. Special attention was paid to possible effects of dipyridamole (chest pain, headache, flushing, bronchospasm, dizziness, nausea, arrhythmia, etc), and aminophylline given to alleviate these effects. Serious AE's were to be reported to the sponsor immediately and a report submitted within 3 working days of its occurrence.

2) Vital signs: Systolic and diastolic blood pressure and pulse were to be obtained at 1- minute intervals beginning one minute prior to infusion of dipyridamole and continuing for 8 minutes following the bolus administration of Myoview or Tl-201.

3) ECG's: A 12-lead ECG is to be obtained at the time of vital signs above, The ECG parameters studied included specifically ST segment deviations, and rhythm abnormalities.

Reviewer's comments: 1) It is not clear how long patients were to be followed for adverse events after injection of Myoview.

2) ECG parameters monitored should include QT and QTc intervals.

3) No monitoring of AE's or vital signs was planned for the resting study.

13) STATISTICAL METHODS (See statistical review by Anthony Mucci, Ph.D.)

A) Safety data: For pulse and systolic BP, paired t-tests were to be used for each tracer to test the null and alternative hypotheses for changes from baseline to maximum values. ANOVA was also to be applied to test effects of each tracer on changes of pulse and systolic BP. (pp. 1125-6)

Reviewer's comment: Diastolic BP is not included in the analysis above, and the sponsor has not provided an explanation for this.

B) Sample size: No calculations were to be performed. The sample size was chosen solely on the ability to recruit suitable patients.

C) Efficacy endpoints: The endpoints chosen for statistical analysis were to be the following (from p. 1122-3 of submission).

- The number of correctly diagnosed SPECT scans as determined by coronary angiography on a subject and vessel level.
- The number of segments demonstrating abnormalities on each scan.
- The number of segments considered in paired rest/stress scans to be normal, fixed, completely reversible or partially reversible.
- The number of segments considered in paired rest/stress scans to be ischemic and/or scar.

D) Efficacy analysis: Data from the blinded readings of both Tl-201 and Myoview SPECT images were to be compared to quantitative angiography results. Subject-, vessel- and segment-based analyses were to be conducted; perfusion defects were to be rated 0 to 3 on the stress images as described in Section #9 above (score of 1 to 3 was abnormal). Reversibility of a perfusion defect was also to be rated from 0 to 3: 0 = non-interpretable, 1 = reversible, 2 = partially reversible, 3 = fixed. Likewise, a vessel with $\geq$50% angiographic stenosis was also to be abnormal; severity rated based on % narrowing (see Section #10).

For subject-based analysis, the individual defect scores were to be used to derive a "sum defect score", "extent of perfusion abnormality" and "mean severity score" (p. 1124 of submission), and these subjected to a non-parametric sign test to compare Tl-201 and Myoview.

For vessel-based analysis, a template of vascular territories was to be laid over the polar map of the Tl-201 or Myoview perfusion scan, and segments assigned to the LAD (#3, 4, 5, 9, 10 and 11); LCx (#1, 2, 7 and 8); and RCA (#6 and 12) as demonstrated on the CRF (p. 1224). From these data, sensitivity,

specificity, predictive values, percent exact agreement and kappa were to be computed for each tracer and each vessel. The apex (segments #13 and 14) was only to be analyzed if an adjacent segment were judged abnormal.

For segment-based analysis, Tl-201 and Myoview scans were to be compared on a segment-by-segment basis. The kappa statistic with 95% confidence interval was to be applied to scores of fixed, partially reversible, reversible or normal for each segment. Ischemia is defined as partial or complete reversibility; scar as partial or no reversibility.

14) STUDY RESULTS

A) Demographics and Baseline Characteristics

The protocol called for enrollment of 25 patients at 2 institutions; 26 were ultimately enrolled, all of whom were evaluable for efficacy. No patients withdrew from the study. Table #10 below summarizes demographic information for the 26 patients in Study #P95-302.

Reviewer's comment: No explanation for the absence of females in this study was given. Without this subset of the population, safety and efficacy claims for Myoview and pharmacologic stress cannot be supported in women by this study.

TABLE #10: DEMOGRAPHIC CHARACTERISTICS (from p. 1129, vol. 5)

Characteristic	N = 26
Age: Mean	62.0
SD	9.48
Range	44.1-75.8
Race: White	25
Black	1
Gender: Male	26 (100%)
Female	0

B) Baseline Cardiac History (p. 1129, vol. 5 of submission)

Tabulations were made for every subject's baseline cardiac history, including location and number of diseased vessels, presence of collaterals and vessel dominance. Table #11 on the next page summarizes this information. Lesions >50% are considered significant for CAD.

C) Dosage and Administration (from Table #10:5, p. 1130 of submission)

All 26 subjects were given two doses of Myoview and one of Tl-201, with mean doses of 7.8, 33.8 and 3.7 mCi, respectively. Table #12 on the next page summarizes this.

TABLE #11: CARDIAC HISTORY (modified from table #10.3, p. 1129, vol. 5)

Characteristic	N = 26 (100%)
Diseased Vessels	
Left Main	6 (23.1%)
LAD	20 (76.9%)
LCx	22 (84.6%)
RCA	19 (73.1%)
Extent of Disease	
1-vessel disease	5 (19.2%)
2-vessel disease	7 (26.9%)
3-vessel disease	14 (53.8%)
Dominance	
Right	22 (84.6%)
Left	4 (15.4%)
Collaterals	
Present	13 (50.0%)
Absent	12 (46.2%)
Missing data	1 (3.8%)

TABLE #12: DRUG EXPOSURE (Table #10:5, p. 1130, vol. 5)

Table 10.5
Exposure to Study Drug

Study Drug	n	Mean	SD	Range (min, max)
Tc-99m tetrofosmin, rest (mCi)	26	7.8	0.20	
Tc-99m tetrofosmin, stress (mCi)	26	33.8	1.40	
Tl-201 (mCi)	26	3.7	0.60	
Dipyridamole using Tc-99m tetrofosmin (mg/kg)	26	0.561	0.0027	
Dipyridamole using Tl-201 (mg/kg)	26	0.560	0.0020	
Aminophylline using Tc-99m tetrofosmin (mg)	21	107	17.9	
Aminophylline using Tl-201 (mg)	17	113	17.9	

SD = standard deviation.

D) Safety Results

1) Adverse Events:

There were no deaths, serious or severe adverse events. According to the table below, 20/26 evaluable patients receiving Myoview (76.9%) experienced a total of 30 AE's in this phase 3 trial. Seventeen of the 26 patients (65.4%) experienced a total of 28 AE's after receiving Tl-201. According to the sponsor, no apparent relationship was seen between the administration of Myoview and frequency of AE's. All AE's were attributed to dipyridamole by the investigators.

The most common adverse events were angina pectoris (11/26 or 42.3% for both Myoview and Tl-201), and headache (9/26 or 34.6% for Myoview and 8/26 or 30.8% for Tl-201), as seen in table #13. No relationships between adverse events and age and race were noted. During Tl-201 stress

tests, 17 patients were given aminophylline (mean dose = 113 mg, range — — mg); during Myoview stress tests, 21 patients received aminophylline (mean 107 mg, range [illegible] mg).

TABLE #13: NUMBER OF PATIENTS WITH ADVERSE EVENTS
(derived from p. 1137, vol. 5 of submission)

Body System	Event Type	Myoview (N=26)	Tl-201 (N=26)
Subjects with >1 AE		20 (76.9%)	17 (65.4%)
Body as a Whole	Headache	9 (34.6%)	8 (30.8%)
	Flushing	4 (15.4%)	2 (7.7%)
Nervous	Dizziness	2 (7.7%)	1 (3.9%)
	Hypoesthesia	1(3.9%)	0 (0%)
	Unspec. ear disorder	1(3.9%)	0 (0%)
	Depersonalization	1(3.9%)	0 (0%)
Cardio-vascular	Angina pectoris	11 (42.3%)	11(42.3%)
	AV block	0 (0%)	1 (3.9%)
	ECG abnormality	0 (0%)	1 (3.9%)
	Hypotension	0 (0%)	1 (3.9%)
Digestive	Nausea	1 (3.9%)	3 (11.5%)

2) Vital Signs (Table #14):

Changes from baseline to peak stress values reflected the effects of dipyridamole, producing significant increases for heart rate and systolic BP, but an insignificant decline in diastolic BP. The increase in heart rate was slightly greater with Myoview (20.0±9.1 mmHg) than with Tl-201 (15.5±9.1 mmHg).

TABLE 14: VITAL SIGNS (From p. 1138, vol. 5 of submission; BL = baseline).

		Heart rate	Systolic BP	Diastolic BP
Tc-99m tetro-fosmin (N=26)	Change from BL	20.0 ± 9.1	7.9 ±13.2	-0.8 ± 6.7
	Range			
Thallium-201 (N=26)	Change from BL	15.5 ±9.1	6.8 ± 10.1	-1.7 + 5.6
	Range			
p-values		0.014	---	0.740

Vital sign changes outside a specified range (>15 bpm for pulse, >20 mm Hg for BP) were noted. For pulse, 16 had increases and 0 decreases of >15 bpm for Myoview and 13 had increases and 0 decreases of >15 bpm for Tl-201, respectively. For systolic BP, 4 had increases and 0 decreases of >20 mm Hg for Myoview and 3 had increases and 0 decreases of >20 mm Hg for Tl-201, respectively. For diastolic BP, 0 had increases and 1 decreases of >20 mm Hg for Myoview and 0 had increases or decreases of >20 mm Hg for Tl-201, respectively. Time points for vital sign measurements post-drug were not specified, but scatterplots (no shift tables) were provided (Safety Response received 7/26/99). These indicated no major concerns.

3) ECG's: According to the sponsor, 9/26 (34.6%) patients had a normal ECG before stress with Myoview, and 10/26 (38.5%) before stress with Tl-201. With stress, 9/26 (34.6%) developed abnormal ST changes (>0.5mm), with both tracers.

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) If 9 patients had an abnormal ECG before Myoview and 10 before Tl-201 stress, one patient would have had to either develop or resolve a resting ECG abnormality between the two tracers. No information was seen in the submission about this change.

E) Efficacy Results

The evaluation of efficacy in this study addressed the endpoints of sensitivity and accuracy for dipyridamole/Myoview SPECT scintigraphy when compared to Tl-201 and coronary angiography as a standard of truth, overall and for the individual coronary arteries, in a database from 26 subjects. Efficacy results were categorized as subject-based, vessel-based and segment-based comparisons of Myoview and Tl-201. Sensitivity, specificity and both predictive values were calculated for the individual vessels, but only sensitivity for CAD overall (all subjects recruited had angiographically documented CAD). Agreement between Tl-201 and Myoview was measured using the kappa statistic. For overall CAD, the sponsor computes a sensitivity of 96% (24/25) for both Tl-201 and Myoview, with one subject unevaluable. For the three individual vessels, the values in Table #15 below were obtained on page 1132 of the submission.

TABLE 15: DIAGNOSTIC EFFICACY (from p. 1132, vol. 5 of submission)

STATISTIC	LAD		LCx		RCA	
Tracer	Tc-99m	Tl-201	Tc-99m	Tl-201	Tc-99m	Tl-201
Sensitivity	35.0	50.0	19.0	13.6	94.4	94.7
Specificity	100.0	50.0	100.0	100.0	20.0	0
Pos. predictive value	100.0	76.9	100.0	100.0	81.0	72.0
Neg. predictive value	19.0	23.1	19.0	17.4	50.0	0
Exact Agreement	32.0	50.0	32.0	26.9	78.2	69.2
Kappa	0.070	0.000	0.070	0.046	0.018	-0.072
95% confidence interval	0.001-0.353	-0.022-0.162	-0.022-0.162	-0.021-0.113	0.266-0.635	0.202-0.057

When subjects are categorized by number of diseased vessels diagnosed angiographically, 1 of 14 patients with 3-vessel disease was missed by both tracers. Four of 5 subjects with 1-vessel and all 7 subjects with 2-vessel disease were all detected as positive with both tracers; one subject with 1-vessel CAD was missed on Myoview because the scan was unevaluable. These data are summarized in Table #16 on the next page:

TABLE 16: SUBJECTS DIAGNOSED WITH CAD BY SPECT PR95-302
(Derived from SAS tabulations, pp. 1904-1907, vol. 8)

# of diseased vessels on angiogram	Normal		Abnormal		Unevaluable	
	Tc-99m n (%)	Tl-201 n (%)	Tc-99m n (%)	Tl-201 n (%)	Tc-99m n (%)	Tl-201 n (%)
1 (n=5)	0 (0%)	0 (0%)	4 (75%)	5 (100%)	1 (25%)	0 (0%)
2 (n=7)	0 (0%)	0 (0%)	7 (100%)	7 (100%)	0 (0%)	0 (0%)
3 (n=14)	1 (7.1%)	1 (7.1%)	13 (92.9%)	13 (92.9%)	0 (0%)	0 (0%)

A table was also generated for the two tracers with respect to vessels with >50% stenosis on angiography vs. the corresponding abnormally perfused vascular territories on SPECT. On 3 occasions, the number of vessels identified as involved was greater on the Tl-201 scan than on angiography; only 1 patient had a Myoview scan showing more vessels to be diseased than seen angiographically. (summarized in Table #17 below).

TABLE #17: DISEASED VESSELS ON SPECT AND ANGIOGRAPHY
(from p. 1134, vol. 5 of submission)

Table 11.3.2B
Subjects with Diseased Vessels by Number of Diseased Vessels Assessed by SPECT Imaging Relative to Coronary Angiography
(Subjects with Evaluable SPECT Images)

By CA	Number of Diseased Vessels Determined by SPECT Imaging													
	Tc-99m tetrofosmin (N = 23)						Tl-201 (N = 26)							
	0		1		2		0		1		2		3	
	N	%	n	%	n	%	n	%	n	%	n	%	n	%
1	0	0.0	3	75.0	1	25.0	0	0.0	2	40.0	3	60.0	0	0.0
2	0	0.0	5	83.3	1	16.7	0	0.0	4	57.1	2	28.6	1	14.3
3	1	7.7	6	46.2	6	46.2	1	7.1	5	35.7	7	50.0	1	7.1

CA = Number of diseased vessels determined by coronary angiography
Percentages shown are based upon number of subjects diagnosed by coronary angiography in each row.

The reason for the discordance in number of subjects between Tl-201 (26) and Tc-99m tetrofosmin (23) is that Myoview SPECT images of three subjects were not evaluable for vessel-based comparisons. Analysis of SPECT images for the two tracers by segment revealed a kappa of 0.53, indicating a moderate level of agreement for evaluating segments as "normal", "reversible", "partially reversible" or "fixed". The 95% confidence interval for kappa was 0.45 to 0.61. For normal vs. abnormal segmental perfusion (where all reversible, partly reversible and fixed defects are combined), kappa was 0.669 (95% confidence interval = 0.585 - 0.754).

Discordant results with the two tracers were seen in 3 patients. One had positive Tl-201 scans but not Myoview; one had different segments (and vascular territories) identified as abnormal in the two studies, and one had a

reversible defect on Tl-201 (but not Myoview) corresponding to a successfully bypassed LAD lesion.

Reviewer's comments: 1) The sensitivity for both tracers was ≤ 50% for LAD disease and < 25% for LCx disease, respectively, while specificity for the RCA was only 20% for Myoview and zero for Tl-201. These poor results most likely reflect the small sample size studied.

2) Since both Tl-201 and Myoview are designed to show relative, rather than absolute perfusion, it is quite possible for a patient with "balanced" 3-vessel disease to have a negative study with either tracer.

14) SPONSOR'S CONCLUSIONS (extracted from pp. 1139-1141 of submission)

- "The study showed that there was no difference between the two agents [Tl-201 and Myoview] in the sensitivity for detection of angiographically proven CAD".
- "Tc-99m tetrofosmin, when used in conjunction with I.V. dipyridamole pharmacologic stress testing, showed high sensitivity for the detection of CAD, similar to that seen with Tl-201".
- "The assessment of number of diseased vessels was similar for both agents, with both agents tending to underestimate the true number of diseased vessels, but with Tl-201 also tending to overestimate the number of diseased vessels relative to coronary angiography".
- "There was moderate to good agreement between the two agents in a segment-by-segment comparison of presence of abnormality, presence of ischemia, or presence of scar".
- "There were no safety concerns noted with the use of Tc-99m tetrofosmin in this study".

[In conclusion] "This study demonstrates that Tc-99m tetrofosmin is safe and efficacious for stress/rest myocardial perfusion imaging when used with I.V. dipyridamole pharmacologic stress testing".

15) REVIEWER'S COMMENTS

A) Trial design and protocol execution:

The design of this trial, a two-center, open-label, crossover type, is appropriate for this Phase 3 investigation. Enrollment was sequential, thus was not truly randomized. The protocol was generally followed in both centers, though a number of changes were made (all listed on pp. 1126-1127). The majority of these changes involved how images were interpreted and scored, but do not alter significantly the overall analysis of efficacy. There were no subject dropouts, though 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 two blinded readers rather than independent reads. The provision of a more detailed timetable would have made it easier to follow the overall study plan.

No explanation was given for the absence of females in this study. Without their inclusion, safety and efficacy claims for Myoview and pharmacologic stress in women cannot be supported by this study.

B) Safety, toxicity and adverse events results:

As Myoview is already approved for use with exercise testing in the diagnosis of CAD, the sponsor felt monitoring of labs (hematology, chemistry and urinalysis) or pulse oximetry was unnecessary (and this reviewer agrees). Nevertheless, the quality of the safety database could be improved. Review of this study report raises a number of specific questions:

1) The followup period for adverse events after injection of Myoview is unclear.
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) It would have been optimal for the sponsor to analyze vital signs and ECG's after the rest injection of Myoview, and compare them to those obtained after the post-dipyridamole stress Myoview injection.
4) Diastolic BP is not included in the safety analysis.
5) The QT(c) interval on the electrocardiogram was not reported; it should be included in the safety database as an important measure of drug toxicity.
6) If 9 patients had an abnormal ECG before Myoview and 10 before Tl-201 stress, one patient would have had to either develop or resolve a resting ECG abnormality between the two tracers. No information was seen in the submission about this change.

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 concordance between angiography results and each tracer was poor, even according to the sponsor.
3) The sponsor has provided no formal image quality assessment in this study.
4) The sensitivity for both tracers was 50% or below for LAD disease and below 25% for LCx disease, respectively, while specificity for the RCA was only 20% for Myoview and zero for Tl-201. These poor results most likely reflect the small sample size studied. They do, however, raise concerns when one considers pharmacologic stress Myoview SPECT as a screening test for CAD.
5) Since both Tl-201 and Myoview are designed to show relative, rather than absolute perfusion, it is quite possible for a patient with "balanced" 3-vessel disease to have a negative study with either tracer.

D) Reviewer's conclusions:

This study does suggest that dipyridamole/Myoview studies may be useful in evaluating suspected coronary artery disease, however, no clear advantages over Tl-201 have been demonstrated. As in Study #P53-006, the sample size was small, but when viewed in combination with Study #P53-006 appears to be adequate to support a revision of Myoview's labeling to include pharmacologic stress. A major drawback in the study design is the use of consensus rather than independent interpretation of images by the blinded readers.

Evaluation of adverse events after the rest injection of Myoview and comparison with AE's experienced following the post-dipyridamole stress Myoview injection would have been ideal. Without this, however, the data provided do show a similar AE profile to that of the stress agent, dipyridamole.

8:5 Reviews of Individual Studies Selected as Supportive to the Claim: Trials from the Literature

8:5:1 Cuocolo 1996

Study Title: "Tc-99m-labeled Tetrofosmin Myocardial Tomography in Patients with Coronary Artery Disease: Comparison between Adenosine and Dynamic Exercise Stress Testing"

Authors: Cuocolo, Nicolai, Soricelli, Pace, Nappi, Sullo, Cardei, Argenziano, Ell, Salvatore

Trial centers: Institute of Nuclear Medicine, University College, London and Universita Frederico II, Napoli, Italy

Reference: *Journal of Nuclear Cardiology* 1996, no. 3, pp. 194-203

1) STUDY OBJECTIVES: This study was conducted "to compare the results of adenosine Tc-99m tetrofosmin SPECT and dynamic exercise stress Tc-99m labeled tetrofosmin SPECT imaging directly in patients with angiographically documented coronary artery disease" (quote, p. 1779, vol. 7 of submission)

2) STUDY DESIGN: This study is a two-center, open-label, triple-administration, non-randomized prospective trial where exercise stress and pharmacologic (adenosine) stress Tc-99m tetrofosmin scintigraphy are compared, with coronary angiography as a truth standard. All subjects underwent *on separate days* three injections of 20 mCi (740 mBq) Tc-99m tetrofosmin (Myoview): rest, a 6-minute adenosine infusion, and bicycle exercise. Safety assessment included vital signs and adverse event monitoring at rest and during the stress test. 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: 41 consecutive patients with known or suspected CAD. Severe HTN, CHF, COPD, asthma, hypotension, 2nd or 3rd degree AV block are exclusion criteria.

5) STRESS PROTOCOL AND MYOVIEW DOSAGE: The protocol called for separate doses of 740 mBq (20 mCi) of Myoview to be given at the rest, exercise and adenosine stress sessions. The three sessions were conducted in random sequence, with imaging visits 3 days apart. For pharmacologic stress, the dose of adenosine was to be 0.142 mg/kg/min I.V. over 6 minutes (consistent with labeling for adenosine). Myoview would be given as an IV bolus after 4 minutes of adenosine infusion. Exercise stress was carried out in a seated position on a bicycle ergometer, according to a standardized multistage protocol, with Myoview injected at 2 minutes before terminating exercise.

6) IMAGE ACQUISITION AND INTERPRETATION: SPECT of the myocardium was acquired in the supine position beginning 30 minutes after each 20 mCi Myoview dose. Thirty-two 64 x 64 pixel images of 40 sec. each were acquired for 180° from RAO to LPO positions. Images were processed without attenuation correction, and reconstructed in the 3 cardiac axes. Slices were then divided into segments (3 short-axis cuts with 6 segments each, and 2 apical segments on the vertical and horizontal long-axis cuts). Uptake in each segment was normalized to the segment with the maximum counts, and expressed as a percentage. Visual inspection was used to evaluate perfusion to a segment: 3 = normal uptake (>70%), 2 = reduced uptake (50-70%), 1 = severely reduced uptake (30-50%), 0 = no uptake (<30%). Side-by-side rest and stress images were then assessed for reversibility. Segments were then assigned a coronary territory for correlation with angiography.

Heart/lung and heart/liver ratios were computed from the anterior images, using mean pixel counts in representative ROI's within each organ. The times after injection of Myoview for this image were not specified.

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

8) BLINDING AND METHODS TO MINIMIZE BIAS: Two investigators read the rest, exercise and adenosine images separately, then reached a consensus. They were blinded to coronary angiography results and corresponding stress image results.

9) CORRELATIVE IMAGING: Coronary angiography was done at a different institution before Myoview scanning (time frame not indicated). Stenoses were measured by an automated edge-detection method, and those of $\geq$50% were considered significant.

10) STATISTICAL METHODS:

A) Safety data: Hemodynamic (BP and pulse) values were reported as mean $\pm$ standard deviation for rest, peak adenosine and peak exercise 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 for paired data was used as well as the chi-square to assess differences between proportions. The relationship between exercise and adenosine Tc-99m tetrofosmin uptake was assessed with linear-regression analysis, and the kappa statistic calculated.

11) STUDY RESULTS

A) Demographics and Baseline Characteristics: 41 patients with suspected or known CAD were enrolled (37 men and 4 women); no mention was made of withdrawals from the study. The patients' mean age was 53 $\pm$ 8 years. No range was given. Twenty-three (23) had a previous MI.

B) Hemodynamic and Safety Results: Hemodynamic parameters (pulse, BP and pressure-rate product) were recorded at rest, exercise and adenosine stress. These are recorded in Table #18 (reproduced on next page from Table #2 in

article). The mean exercise workload was 90 ± 24 watts; mean duration was 7 ± 2 minutes. Means and standard deviations were given for pulse, BP and pressure-rate product at baseline and peak values for exercise and adenosine infusion. No mention was made of prematurely stopping adenosine. Chest pain was experienced by 10 patients (24%) with exercise and 12 (29%) with adenosine. ST-segment depression on ECG was seen in 12 (29%) with exercise and 6 (15%) with adenosine. During exercise, severe angina developed in 10/41 patients (24%). During adenosine infusion, 31/41 patients experienced mild symptoms (flushing, dizziness, lightheadedness, transient chest discomfort, dyspnea which resolved in <2 min. after stopping adenosine).

TABLE #18: Hemodynamic Parameters (Derived from Table #2, p. 2038, vol.9)

Parameter	Exercise		Adenosine	
	Baseline	Peak	Baseline	Peak
Heart rate	77 ± 10	138 ± 17	72 ± 11	88 ± 16
Systolic BP	126 ± 15	176 ± 21	130 ± 16	131 ± 20
Diastolic BP	79 ± 10	97 ± 10	80 ± 10	77 ± 12
Pressure-rate product	9,252 ± 2,985	22, 931 ± 7,039	9,186 ± 2,524	11,229 ± 3,413

C) Efficacy Results

The evaluation of efficacy in this study comprised a measure of sensitivity, specificity and diagnostic accuracy of Tc-99m tetrofosmin SPECT for diagnosing CAD, under exercise and pharmacologic stress conditions. Overall, 902 cardiac segments in 41 patients were studied.

Overall, 34/41 patients with documented CAD were found to have an abnormal exercise Myoview SPECT scan (sensitivity = 84%), while 35/41 had an abnormal adenosine/Myoview SPECT scan (sensitivity = 86%). (See Table #19 and 20 below). Sensitivity and specificity for detection of stenoses was also reported for infarcted (27 segments) and viable (96 segments) territories, for both exercise and adenosine stress Myoview SPECT. (See Table #21, next page). The differences between exercise and adenosine sensitivities and specificities for detecting stenoses were not significant for viable or infarcted segments.

TABLE #19: Diagnostic Accuracy: Exercise Stress (RCA = PDA in original tables)

STATISTIC	LAD	LCx	RCA	All vessels
Sensitivity	85%	88%	81%	84%
Specificity	100%	92%	90%	92%
Overall accuracy	88%	90%	85%	88%

TABLE #20: Diagnostic Accuracy: Adenosine Stress (RCA = PDA in original tables)

STATISTIC	LAD	LCx	RCA	All vessels
Sensitivity	91%	88%	76%	86%
Specificity	100%	92%	70%	85%
Overall accuracy	93%	90%	73%	85%

TABLE #21: Diagnosis of CAD in Infarct and Viable Zones

STATISTIC	Infarcted zones		Viable zones	
	Exercise	Adenosine	Exercise	Adenosine
Sensitivity	88%	96%	83%	80%
Specificity	100%	100%	92%	84%

Agreement between adenosine and exercise SPECT studies was 100% with respect to normal vs. abnormal findings (1 normal, 40 abnormal patients), and 85% with respect to localizing a perfusion defect to a specific vascular territory. In addition, agreement between exercise and adenosine stress was reported for segmental uptake scores and for presence of reversible or fixed defects within a segment, and kappa values calculated. The agreement data was presented as a 4x4 table for regional uptake scores and a 3x3 table for normal vs. reversible vs. nonreversible segments. (See Tables #22 and 23 below, derived from Figures #2 and 3, pp. 199-200 of paper, pp. 2039-2040, vol. 9 of submission).

TABLE #22: Uptake Score Agreement

Myoview Adenosine \ Myoview Exercise	2	1	0
1	5	21	0
15	55	10	1
45	31	0	2
47	1	0	3

Agreement = 737/902
Kappa = 0.66 ± 0.02

TABLE #23: Reversibility Agreement

Myoview Adenosine \ Myoview Exercise	Normal	Reversible	Fixed
Normal	548	23	13
Reversible	26	62	11
Fixed	8	12	199

Agreement = 809/902
Kappa = 0.80 ± 0.02

Heart/lung ratios were similar for exercise and adenosine stress Myoview SPECT: 2.9±0.7 vs. 2.7±0.5 respectively (not significant). Comparison of defect size between the two studies showed them to be similar: 36%±23% for exercise vs. 37%±22% for adenosine. The severity of uptake reduction within corresponding abnormally perfused segments was slightly greater for exercise (52%±14%) than for adenosine (55%± 14%), $p < 0.01$. For heart/liver ratios, corresponding values for exercise and adenosine were 0.6 ± 0.2 and 1.2 ± 0.4, respectively ($p < 0.001$).

13) AUTHOR'S CONCLUSIONS: "Despite different hemodynamic effects, adenosine and dynamic exercise Tc-99m tetrofosmin SPECT imaging provides similar information in the diagnosis and localization of CAD." (quote, abstract, p. 1778)

14) 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 direct comparison of exercise and adenosine Myoview SPECT images acquired under otherwise identical conditions (Myoview dose, time after imaging, SPECT acquisition parameters). Patients were enrolled prospectively and consecutively

(inclusion and exclusion criteria were specified), and there was a detailed description of dosing, acquisition and processing procedures. The study compared both exercise and adenosine Tc-99m tetrofosmin SPECT to coronary angiograms as a truth standard. Evaluation of efficacy was compared on a patient-by-patient as well as a segment-by-segment basis. Importantly, readers of rest, exercise and adenosine SPECT images were blinded to angio results.

B) Design limitations: This study was one of the more significant literature trials provided by the sponsor to support the use of Myoview with adenosine stress. The sample size was small (41 patients), though this study is more robust than some conducted by the sponsor. With only one subject with normal coronaries, a selection bias is apparent. This reduces the value of this study's support of adenosine Myoview SPECT as a screening test for CAD.

Criteria for evaluating image quality were not defined. (except for heart/lung and heart/liver ratios). No mention was made if the Myoview SPECT readers were blinded to patient history. Readers of the angiograms ideally should also be blinded to history and Myoview scan results, but no mention was made of this. The time between angiography and Myoview SPECT was also not reported. The two blinded readers also reached a consensus, which does not have as much credibility as independent blinded reads.

PPV and NPV were not reported for CAD patients as a whole, for each segment or for each coronary artery. For the sensitivity, specificity and accuracy data in Tables #2-4 of the article, the numbers of stenosed vessels (n) were not given for each percentage reported.

Seven of the 26 patients reported here were also enrolled in a subsequent study by this investigator (Cuocolo 1997), reducing the total number of subjects in the efficacy database available from the literature submitted.

Rest and stress Myoview scans were done on separate days unlike the same-day protocol indicated in the proposed labeling.

C) Reviewer's conclusions:

The results of this study indicate comparable and acceptable sensitivity, specificity and accuracy for both exercise and adenosine/Myoview SPECT in diagnosing and localizing CAD, but exercise was somewhat better than adenosine in the RCA distribution (81% vs. 76% sensitivity, 90% vs. 70% specificity). One possible explanation for this, in the opinion of this reviewer, is the lower heart/liver uptake ratio for adenosine, which directly influences the ability to read the RCA territory on the Myoview images. The aim of this study was not to evaluate the true diagnostic potential of Myoview but to compare pharmacologic stress using adenosine to exercise stress. Nevertheless, the use of consensus rather than independent blinded reading of images reduces the study's supportive value. In addition, unlike the 1-day protocol in the proposed labeling, this study used rest and stress Myoview scans done on separate days. This is not expected to adversely influence the clinical usefulness of Myoview and pharmacologic stress. Adverse events and vital sign changes for the 41 patients reflected the exercise and adenosine stress experienced.

8:5:2 Cuocolo 1997

Study Title: "Adenosine Coronary Vasodilatation in Coronary Artery Disease: Technetium-99m-labeled Tetrofosmin Myocardial Tomography versus Echocardiography"
Authors: Cuocolo, Sullo, Pace, Nappi, Gisonni, Nicolai, Trimarco, Salvatore
Center: Center for Nuclear Medicine of the CNR, Universita Frederico II, Napoli, Italy
Reference: ***Journal of Nuclear Medicine 38,*** **1997, no. 7, pp. 1089-1094**

1) STUDY OBJECTIVES: This study was conducted "to compare the results of adenosine Tc-99m tetrofosmin cardiac tomography with those of adenosine echocardiography in identifying patients with CAD and in localizing individual stenosed coronary vessels" (quote, p. 1788, vol. 7 of submission)

2) STUDY DESIGN: This study is a single-center, open-label, double-administration, non-randomized prospective trial where pharmacologic (adenosine) stress Tc-99m tetrofosmin (Myoview) scintigraphy and adenosine echocardiography are compared, with coronary angiography as a truth standard. All subjects underwent *on separate days* two injections of 20 mCi (740 mBq) Myoview: at rest and 4 minutes into a 6-minute adenosine (0.14 mg/kg/min) infusion. During this infusion, 2-dimensional echocardiographic images of the left ventricle in standard projections were acquired, beginning before and continuing to 6 minutes after withdrawal of adenosine. Thirty minutes after each Myoview injection, SPECT of the heart was acquired. Scintigrams, echocardiograms and angiograms were interpreted separately by two readers blinded to results of the other two modalities. The two readers then reached a consensus. Safety assessment included vital signs, ECG's and adverse event monitoring at rest and during adenosine infusion. Efficacy endpoints included concordance between echo and Myoview scans as well as sensitivity, specificity and accuracy of the 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: 26 consecutive patients with known or suspected CAD. Severe HTN, CHF, COPD, asthma, hypotension, 2nd or 3rd degree AV block are exclusion criteria.

5) ADENOSINE INFUSION AND MYOVIEW DOSAGE: The protocol called for a dose of 740 mBq (20 mCi) of Myoview to be given on separate days at rest and during the adenosine infusion. For pharmacologic stress, the dose of adenosine was to be 0.142 mg/kg/min I.V. over 6 minutes (consistent with the labeling for that drug). Myoview would be given as an IV bolus after 4 minutes of adenosine infusion.

6) SPECT IMAGE ACQUISITION AND INTERPRETATION: SPECT of the myocardium was acquired in the supine position beginning 30 minutes after each 20 mCi

Myoview dose. SPECT parameters are described in detail in the article and are similar to those in Cuocolo 1996. Uptake in a segment was considered abnormal if > 2 s.d. below the mean for that segment in a reference normal population. A segment with reduced activity was considered fixed if uptake in that segment was <10% greater on resting images. Segments were then assigned a coronary territory for correlation with contrast angiography.

7) ECHOCARDIOGRAPHY: 2-dimensional echocardiographic images of the left ventricle in standard projections were obtained, beginning before and continuing to 6 minutes after, withdrawal of adenosine. Images were acquired using a wide-angle phased array sector scanner with a 2.4 mHz transducer. A video record, at 60 frames/sec., was made on SVHS tape. Two blinded readers interpreted the images: segmental wall motion was scored 1 = normal to 4 = dyskinetic. A positive study for ischemia was represented by appearance of or worsening of a wall motion abnormality with adenosine infusion. Infarction was represented by a fixed reduction in wall motion.

8) BLINDING AND METHODS TO MINIMIZE BIAS: Two nuclear medicine physician investigators read the side-by-side rest and stress images to assess reversibility. They were blinded to clinical history, echocardiographic and contrast coronary angiography results, but reached a consensus interpreting the scintiscans.

9) CORONARY ANGIOGRAPHY was done at a different institution up to 4 weeks before Myoview scanning, using a Judkins catheter. Images were interpreted by two independent, blinded readers. Stenoses of $\geq$50-75% were considered moderate; those of >75% were read as severe.

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

11) STATISTICAL METHODS:
   A) Safety data: Hemodynamic (BP and pulse) values were reported as mean $\pm$ 1 standard deviation for baseline and peak adenosine stress values.

   B) Efficacy data: Descriptive statistics were reported for relationships between scintigraphic and angio findings (sensitivity, specificity and accuracy). The Student's T-test for paired and unpaired data was used to assess differences between proportions. The Fishers exact and McNamar tests were applied to frequency data. Relationships between adenosine echo and adenosine Myoview uptake were assessed using the kappa statistic and its standard error.

12) STUDY RESULTS
   A) Demographics and Angiographic Results:
      Twenty-six patients with suspected or known CAD were enrolled (24 men and 2 women); no mention was made of withdrawals from the study. The patients' mean age was 52 $\pm$ 10 years. No range was given. Six (23%) had a

previous MI. Coronary angiography indicated 25 patients (96%) of these to have a stenosis of ≥50% in at least 1 vessel. One patient had normal coronaries; 12 had 1-vessel, 7 had 2-vessel and 6 had 3-vessel disease. There were 13 vessels with moderate stenoses in 11 patients and 31 vessels with severe stenoses in 22 patients.

Seven of the 26 patients reported here were also enrolled in a previous study by this investigator (Cuocolo 1996).

B) Hemodynamic and Safety Results: Means and standard deviations were given for heart rate, BP and pressure-rate product at baseline and peak values for the adenosine infusion These are recorded in Table #24 (reproduced from Table #2 in article). During adenosine infusion, 17 patients (65%) experienced mild and transient adverse effects. Chest pain was experienced by 9 patients (36%), and ischemic changes on ECG were seen in 3 (11%). During adenosine infusion, 5 (30%) of the patients experienced flushing, 2 (10%) dizziness or lightheadedness, and 1 (6) dyspnea. No mention was made of prematurely stopping adenosine.

TABLE #24: Hemodynamic Parameters (Derived from Table #2, p. 2046, vol. 9)

Parameter	Adenosine Stress	
	Baseline	Peak
Heart rate	73 ± 12	91 ± 18
Systolic BP	130 ± 18	129 ± 19
Diastolic BP	81 ± 11	75 ± 11
Pressure-rate product ($x10^3$)	9.6 ± 2.3	11.7 ± 3.0

C) Efficacy Results

The efficacy assessments in this study were the sensitivity, specificity and diagnostic accuracy of adenosine Tc-99m tetrofosmin SPECT and adenosine 2-D echocardiography for diagnosing CAD. A total of 78 vascular territories in 26 patients were studied. (See Table #25 and #26 on the next page).

Overall, 22/25 patients with documented CAD were found to have an abnormal adenosine Myoview SPECT study (sensitivity = 88%), while 17/25 had an abnormal adenosine echocardiogram (sensitivity = 68%). Both studies were normal in the one patient with normal coronaries. Agreement between the two studies in overall CAD diagnosis was seen in 21 patients (84%); kappa = 0.45 ± 0.18. Sensitivity and specificity for detection of stenoses were also reported for single-vessel (12 patients) and multivessel (13 patients); these were reported for both adenosine stress Myoview SPECT and echocardiography. (See Table #27, next page). Adenosine Myoview SPECT demonstrated significantly better sensitivity, specificity and accuracy for detecting stenoses than echocardiography in patients and all 3 individual vascular territories. (Derived from Table #3, page 2047, vol. 9)

TABLE #25: Diagnostic Accuracy: Adenosine Myoview Scan
(RCA = PDA in original tables) n = 78 vascular territories

STATISTIC	LAD	LCx	RCA	All vessels
Sensitivity	81%	83%	73%	79%
Specificity	100%	86%	87%	88%
Overall accuracy	85%	85%	81%	83%

TABLE #26: Diagnostic Accuracy: Adenosine Echocardiogram
(RCA = PDA in original tables) n = 78 vascular territories

STATISTIC	LAD	LCx	RCA	All vessels
Sensitivity	57%	50%	64%	57%
Specificity	80%	64%	67%	68%
Overall accuracy	61%	58%	65%	61%

TABLE #27: Diagnosis of Single-vessel (n=12) and Multivessel (n=13) CAD

STATISTIC	Single-vessel disease		Multivessel disease	
	SPECT	Echo	SPECT	Echo
Sensitivity	83%	75%	78%	50%
Specificity	87%	62%	86%	71%
Overall accuracy	86%%	67%	79%	54%

Eighteen of 22 patients with perfusion defects were found to have reversibility; 14 of 17 with abnormal echo were found to have a reversible wall-motion abnormality. Sensitivities for detecting moderate stenoses of 50-75% were 46% and 77% for echo and SPECT, respectively. For detecting severe (>75%) stenoses, sensitivity for echo was 61% and for SPECT 81%.

13) AUTHOR'S CONCLUSIONS: "This study demonstrates that adenosine-induced maximal coronary vasodilatation associated with quantitative Tc-99m tetrofosmin cardiac tomography is more accurate than adenosine two-dimensional echocardiography to identify patients with CAD and localize individual stenosed coronary vessels." (quote, p. 1793, vol. 7)

14) REVIEWER'S COMMENTS:

A) Design strengths: The study has many design features in common with the previous study by this author (Cuocolo 1996), and consequently, many of the same strengths and weaknesses. This paper was the only direct comparison of Myoview SPECT images with echocardiograms acquired under identical clinical conditions (infusion of adenosine). Patients were enrolled prospectively and consecutively (inclusion and exclusion criteria were specified), and there was a detailed description of dosing, acquisition and processing procedures. The study compared both exercise and adenosine Tc-99m tetrofosmin SPECT to coronary angiograms as a truth standard. Evaluation of efficacy was compared on a patient-by-patient as well as a vessel-by-vessel basis. Importantly, readers of each of the three modalities: SPECT, ultrasound and angiographic images,

were blinded to clinical data and results of the other two modalities. In each case a third reader (also blinded) would review the images if the original ones did not agree.

B) Design limitations: Though this study was one of several literature trials provided by the sponsor to support the use of Myoview with adenosine stress, some deficiencies remain. The sample size was small (26 patients), and analysis of vascular territories (3 per patient) does not add to the power of the study. With only one subject with normal coronaries, a selection bias is apparent. This reduces the value of this study's support of adenosine Myoview SPECT as a screening test for CAD.

As in Cuocolo 1996, rest and stress Myoview scans were done on separate days, unlike the same-day protocol in the proposed labeling.

Criteria for evaluating echocardiogram and SPECT image quality were not defined; all images were simply judged as adequate.

The blinded readers also reached a consensus in interpreting the scans, which does not have the supportive value of independent reads.

PPV and NPV were not reported for CAD patients as a whole or for each coronary artery. For sensitivity, specificity and accuracy data in Tables #24-25, the numbers of angiographically stenosed vessels (n) in each location (LAD, LCx, RCA) were not given (the denominator used to compute each percentage).

Seven of 26 patients reported here were also enrolled in the previous study by this investigator (Cuocolo 1996), reducing the total number of subjects (60) in the efficacy database available from the literature provided.

C) Reviewer's conclusions: Despite the small sample size, the results of this study indicate sensitivity, specificity and accuracy for adenosine/Myoview SPECT to be significantly higher than adenosine/echocardiography in diagnosing and localizing CAD, both for patients as a whole and for the individual vessels. One possible explanation for this, in the opinion of this reviewer, is that LV dysfunction is a less sensitive indicator of a coronary stenosis than a perfusion abnormality on a radionuclide scan. Because rest and stress Myoview scans were done on separate days, this study does not reflect the proposed labeling revisions, which call for both rest and pharmacologic stress scans to be done the same day. However, these shortcomings are not expected to adversely influence the clinical usefulness of Myoview in the setting of pharmacologic stress. Nevertheless, the use of consensus rather than independent blinded reading of images reduces the study's supportive value.

With respect to safety, adverse events and hemodynamic changes reported here largely represent those typically seen with adenosine infusion. Due to the overlap of 7 patients between the two studies by Cuocolo et. al., only the larger of the trials (Cuocolo 1997: 41 patients) was included in the suggested labeling revisions.

9: Overview of Efficacy:

9:1 Introduction:

After review of the two pivotal studies conducted by the sponsor and the two studies by Cuocolo et. al, it has become clear that although the individual sample sizes were small, the combined results suggest that Myoview may be useful in the evaluation of CAD in those unable to exercise adequately. Efficacy results from Studies #P53-006 and PR95-302 were obtained from a total of 84 patients undergoing dipyridamole stress. The two remaining literature studies have provided a combined sample of 60 additional patients to be evaluated for adenosine stress. Despite the use of different trial designs, patient populations and endpoints, the data are in agreement with extensive exercise stress Myoview experience to date. A discussion of design characteristics in each of the 4 trials above follows in Section #9:2; sensitivity and specificity results are discussed in #9:3 to 9:7; and image quality in #9:8.

9:2 Reviewer's evaluation of trials in support of efficacy

9:2:1 Sponsor's pivotal trials (dipyridamole)

The trial designs of pivotal studies #P53-006 and PR95-302 were described in section #8:1, page 10. The general design of each study was adequate; the principal flaw was the differences between the two studies making it difficult to pool data and increase statistical robustness. A flaw in both trials was use of consensus reads, which do not have as much credibility as independent blinded reads. The major differences included different populations (#53-006 included patients *suspected* of having CAD; #PR95-302 only enrolled patients with *documented* CAD), and the use of thallium-201 as a comparator in Study #PR95-302 but not in #P53-006. Also, Study #PR95-302 did not include any formal evaluation of SPECT image quality, while Study #P53-006 included at least a subjective assessment of overall image quality. The use of coronary angiography as a truth standard is a significant strength of study design.

1) Study #P53-006: The design of trial #P53-006, a multi-center, open-label, non-randomized type, was appropriate as a Phase 3 pivotal study. The trial was conducted to determine sensitivity, specificity and predictive accuracy of dipyridamole/Myoview imaging against coronary angiography, an appropriate truth standard. There were no subject dropouts, however, both efficacy and safety data was missing from a number of subjects. The sample size of 58 evaluable subjects with known or suspected CAD is small to begin with. The study utilized blinded interpretation of images for primary efficacy assessment, though final interpretation was by consensus of the three blinded readers rather than independent reads.

2) Study #PR95-302: The design of trial #PR95-302, a two-center, open-label, crossover type, was also appropriate. Unlike #53-006, this trial was conducted to compare Tl-201 with Myoview against coronary

angiography as a truth standard. The sample size is again small (26 subjects with documented CAD); this is perhaps the trial's biggest drawback. Certainly, as a "stand-alone" trial comparing Myoview to Tl-201, this is inadequately powered to support the indication. The study utilized blinded reading of SPECT images for primary efficacy assessment, though interpretation was again by consensus of the two blinded readers rather than independent reads. Given the guidelines in the 1998 Draft Guidance for blinded reads, this is a major drawback.

Both studies used dipyridamole, an approved agent of pharmacologic stress, but they provide no data to support the use of Myoview with adenosine or other stress agents.

9:2:2 Literature trials (adenosine)

A discussion of the two studies from the literature selected as possibly supportive of the pharmacologic stress claim follows. Each trial was evaluated by this reviewer in light of criteria listed in the *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products*. The design of these studies is discussed below:

1) Cuocolo 1996: Though not an inherent design flaw, imaging at rest and after adenosine stress on different days does not reflect the one-day protocol specified in the proposed labeling. The small sample size of 41 only includes 1 subject with normal coronaries; a selection bias is apparent. Seven patients also participated in the Cuocolo 1997 study, reducing the combined sample size for both studies.

No mention was made if the Myoview SPECT readers were blinded to patient history, but readers of exercise stress images were blinded to adenosine stress scan results and vice versa. Readers of the angiograms ideally should also be blinded to history and Myoview scan results, but no mention was made of this. The blinded readers reached a consensus rather than reading scans independently. In addition, the time between angiography and Myoview SPECT was not reported and criteria for image quality were not defined (except for heart/lung and heart/liver ratios).

PPV and NPV were not reported for CAD patients as a whole, for each segment or for each coronary artery. For sensitivity, specificity and accuracy data, the numbers of stenosed vessels (n) were not given for each percentage reported.

2) Cuocolo 1997: As in Cuocolo 1996, imaging at rest and after adenosine stress on different days does not reflect the one-day protocol specified in the proposed labeling. The sample size of 26 is small, and analysis of vascular territories (3 per patient) does not add to the power of the study. Seven patients were also enrolled in the 1996 study, reducing the sample size to 60 for the two studies together and database as a whole. The larger of these trials (1996) was chosen for labeling. This sample size may still provide sufficient statistical power to be supportive of the revised

labeling of Myoview. Nevertheless, with only 1 subject having normal coronaries, a selection bias is apparent. This reduces the value of this study's support of adenosine Myoview SPECT as a screen for CAD.

As in Cuocolo 1996, blinded readers reached a consensus rather than independent read, and criteria for evaluating echo and SPECT image quality were not defined; all images were simply judged adequate.

PPV and NPV were not reported for CAD patients as a whole or for each coronary artery. For sensitivity, specificity and accuracy, the numbers of angiographically stenosed vessels (n) in each location (LAD, LCx, RCA) weren't given (denominator used to compute each percentage).

In summary, the two studies from the literature have limitations as described above, but do offer some supplementary support for the revised labeling for Myoview proposed in this Supplement. The use of consensus rather than independent blinded reading of images further reduces the studies' supportive value. Results of these studies and pivotal trials P53-006 and PR95-302 are summarized below.

9:3 Sensitivity and Specificity Results: Table #28 below lists sensitivities and specificities for the two pivotal trials P53-006 and PR95-302 as well as both trials by Cuocolo et. al. Overall sensitivity for CAD by subject ranged from 92% to 100% and by vessel from 48 to 86%. Overall specificity by subject ranged from 31% to 100% and by vessel from 50% to 88%. For individual vessels, sensitivity ranged from 19% for the LCx in PR95-302 to 96% for the RCA in P53-006. Specificity for individual vessels ranged from 20% for the RCA in PR95-302 to 100% for the LAD in three studies.

(derived from Table #1.1, p. 1641, vol. 7)

TABLE #28: SENSITIVITY AND SPECIFICITY OF MYOVIEW

Study	No. of Subjects	Pharmacologic Stress Agent	Sensitivity/Specificity (%)				
			LAD	LCx	RCA	Overall Vessel	Overall Subject
P53-006	58	Dipyridamole	71/44	40/79	96/25	70/50	96/31
PR95-302	26	Dipyridamole	35/100	19/100	94/20	48/71	96/ns
Cuocolo '96	41	Adenosine	91/100	88/92	76/70*	86/85	100/100
Cuocolo '97	26	Adenosine	81/100	83/86	73/87*	79/88	92/100

ns = not specified * = Posterior descending artery (PDA)

9:4 Efficacy Results of Dipyridamole Study P53-006:

Study #P53-006 enrolled 64 subjects, all of whom were dosed and 58 were evaluable. Results of sensitivity, specificity, PPV, NPV and accuracy as well as kappa statistics for agreement between Myoview and angiography were presented in four tables on pp. 1839-1842, vol. 8 of the submission. These results, along with Reviewer's Efficacy Comments, were presented in Section #8:2: Reviews of Individual Studies.

9:5 Efficacy Results of Dipyridamole Study PR95-302:

Study #PR95-302 enrolled 26, all of whom received Myoview and were evaluable. Tl-201/dipyridamole scans were compared to Myoview/ dipyridamole scans with respect to sensitivity for detecting CAD. The two tests both gave a subject-based sensitivity of 96%: 25/26 subjects with abnormal angiograms (≥50% stenosis) had abnormal SPECT studies with each tracer. Results of sensitivity, specificity, PPV, NPV and accuracy as well as kappa statistics for agreement between Myoview and angiography in each vessel were presented in three SAS tables on pp. 1908-1913, vol. 8 of the submission. These were also summarized in Section #8:2.

When subjects are categorized by number of diseased vessels diagnosed angiographically, one of 14 patients with 3-vessel disease was missed by both tracers. Four of 5 subjects with 1-vessel and all 7 subjects with 2-vessel disease were read as positive with both tracers; the one subject with 1-vessel CAD was missed on Myoview because the scan was unevaluable. These data and Reviewer's Comments are also presented in Section #8:2.

9:6 Efficacy Results of Adenosine Studies (both trials from the literature)

Efficacy results for adenosine are reviewed from the two trials by Cuocolo et. al. in the literature; no trials were conducted by the sponsor. Results were reported as sensitivity and specificity of adenosine/Myoview scans as compared to angiography. Again, data could not be pooled, but sensitivities for CAD ranged from 79 to 86% and specificities, 85 to 88%.

9:7 Efficacy Results of Study with Multiple Stress Agents (PR96-301)

This sponsor-conducted trial did not compare Myoview scintigraphy with a standard of truth (i.e. coronary angiography), and was not intended to provide pivotal support to the pharmacologic stress indication for Myoview. Subjects underwent Myoview imaging with exercise, dipyridamole, adenosine and dobutamine on separate days. Myocardial segments were scored on a scale of 0 to 4 (normal to absent activity) for perfusion and reversibility. The results are presented in Appendix #3 of the MOR.

9:8 Image Quality Results of Three Studies: (from Page 1642, vol. 7)

Image quality, when reported, was according to a semiquantitative, subjective scale. Study PR94-304 included 50 subjects undergoing rest Tl-201 and stress Myoview studies: "Excellent" or "good" ratings were given to 98% of the Tl-201 scans and 94% of the Tc-99m tetrofosmin scans, respectively. Study P53-006 reported 55 of 64 (86%) of the subjects to have "good" or better Myoview scans. All were "interpretable". One of 26 Myoview scans in Study PR95-302 was unevaluable.

10: Overview of Safety: Source: Integrated Summary of Safety (ISS), vol. 6.

10:1 General

The safety database for this NDA supplement includes 5 trials by the sponsor, 8 from the literature (6 in the ISE and 2, non-ISE), 4 foreign non-IND trials and 1 ——— stress study. Emphasis was placed on Studies #PR95-302, PR94-304 and PR98-301 by the sponsor, as data from these trials could be pooled for analysis. Data from the other studies was reported separately. Raw data was accessible for the five studies conducted by the sponsor. Safety parameters evaluated include adverse event (AE) monitoring in all five studies by the sponsor, and vital signs and ECG's in all studies except #PR94-304, where only AE monitoring was carried out. AE monitoring was carried out beginning with the administration of the respective pharmacologic stress agent. None of the study reports indicated clearly how long such monitoring continued after the stress imaging procedure, and none of the protocols called for AE and vital sign monitoring following the rest Myoview injection. Under the categories of AE's, vital signs and ECG's, safety information is presented for the sponsor's trials, literature trials and additional safety data for non-IND studies conducted by the sponsor. These trials are summarized in Table #29 below.

TABLE #29: TRIALS IN SAFETY DATABASE (Sponsor's trials)
Source: prepared by this reviewer for fileability meeting of 4/7/99

TRIAL	P53-006	PR95-302	PR94-304	PR98-301	PR96-301
Stress agent and dose	Dipyridamole 0.56 mg/kg up to 60 mg	Dipyridamole 0.56 mg/kg	Adenosine, dipyridamole or dobutamine* Dose data not available	Adenosine (271 pts) or dobuta-mine* (13 pts) Dose according to protocol at each study site	Dipyridamole + adenosine + dobutamine* See Appendix #3 for dose
Pts. enrolled pts. dosed	64 64	26 26	64 60	284 283	49 48
Myoview dose	5-8 mCi and 15-24 mCi	5-8 mCi and 25-35 mCi	25 mCi.	5-8 mCi and 15-24 mCi	0.36 mCi/kg x 4 (max. of 42 mCi)
Dose of comparator (i.e. Tl-201)	---	Tl-201 3mCi	Tl-201 3mCi	---	---
Adverse events	43/64 (67%)	20/26 (77%)	16/64 (25%)	241/284 (85%)	44/49 (90%)
Safety endpoints	ADE's, vital signs (VS) ECG's pre- to 15 min. post-stress. Length of followup unclear Aminophylline administration	ADE's Vital signs ECG's pre-during and post-stress Length of followup unclear	ADE's only. Length of followup unclear	ADE's to 24 hours VS's, ECG's at baseline, during stress & at 24 hours	ADE's to 24 hours VS's, ECG's at baseline, during imaging and 24 hours

*Agent not approved for stress by FDA