Reviewer's comment: The absence of AE monitoring after the resting Myoview injection renders it impossible to determine whether an AE is related to administration of Myoview or the respective pharmacologic stress agent. This is a serious limitation, however, it could be potentially overcome by Myoview's safety profile to date and comparison of data collected to the AE profile for approved pharm/stress agents.

The sponsor has chosen the clinical trials PR95-302, PR94-304 and PR98-301 to provide the principal data in support of the safety of Myoview in subjects exposed to a single pharmacologic stress agent. Study PR96-301 provides the safety data for Myoview in subjects exposed to multiple stress agents as well as exercise. The sponsor has analyzed the single- and multiagent (3 stress agents given consecutively to each patient) studies separately. Differences in the timing of AE, vital sign and ECG monitoring among the trials makes pooling the data from these studies difficult.

The sponsor has also reported safety data from 6 of the 7 studies in the literature submitted by the sponsor in support of efficacy. These studies involved a total of 603 patients undergoing pharmacologic stress and imaging with Myoview. These data are summarized under the following subsections under demographics, Myoview exposure, AE's, vital signs and ECG's. AE's were not reported for Mahmood (1995) in their 25 patients.

Finally, the ISS includes reports of safety results from 4 foreign non-IND trials by Nycomed Amersham, a study using [redacted] stress, and data from 2 additional articles in the literature but not included in the efficacy analysis (Section #10:7).

10:2 Demographics in the Safety Database (Table #30, next page)

10:2:1 Single Stress Agent Studies PR98-301, PR95-302, P53-006, PR 94-304 (Source: SAS tabulations, pp. 1421-1428, vol. 6)

There were 438 subjects enrolled; safety data is reported in Table #29. Height and body surface area figures were not recorded. 15 patients from the 4 studies were withdrawn prior to drug administration, leaving 423 available for efficacy analysis. All 438 patients are included in the safety (intent-to-treat) analysis.

10:2:2 Multiple Stress Agent Study PR96-301 (Source: SAS tabulations, pp. 1429-1430, vol. 6)

There were 49 subjects; safety data is reported in Table #30 on the next page. Ten patients from Study #PR96-301 withdrew after exercise stress and 1 was lost to followup, leaving 38 patients for efficacy analysis. All 49 are included in the safety (intent-to-treat) analysis.

10:2:3 Demographics in the Literature Studies

A total of 603 patients undergoing pharmacologic stress and imaging with Myoview (433 males, 170 females). Mean ages for the studies ranged from 53 for Cuocolo 1996 to 67 for Takeishi 1998. Race and weight information was not available.

TABLE #30: DEMOGRAPHIC CHARACTERISTICS (Sponsor's trials)
(derived from p. 1375, 1377, vol. 6)

Characteristic	Single stress agent	Multi-stress agent	Combined
N	438	49	487
Age (N)	436 (2 missing)	49	485
(yrs) Mean	65.4	58.7	64.7
SD	12.51	11.5	--
Range	27-97	33.9-81.1	27-97
Gender (N)	438	49	487
Male	232 (53%)	44 (90%)	266 (55%)
Female	205 (47%)	5(10%)	210 (45%)
Missing	1 (0.2%)	0	1
Race White	273 (62%)	35 (71%)	308 (70.3%)
Black	73 (17%)	3 (6%)	76 (17.4%)
Hispanic	15 (3%)	10 (20%)	25 (5.7%)
Asian	6 (1%)	0	6 (1.4%)
Other	6 (1%)	1 (2%)	7 (1.6%)
Missing/unavail.	65 (15.2%)	0	65
Weight (N)	334	49	383
(kg.) Mean	84.95	82.33	84.61
SD	22.18	13.69	--
Range	39.5-209.1	56.8-117.2	39.5-209.1

10:3 Dosing and Extent of Myoview Exposure

A total of 481 subjects/patients were given at least one dose of Myoview in trials conducted by the sponsor. Of these, 433 received Myoview in 4 single-stress agent studies (423 received the stress agent); and 48 in one multi-agent study. The overall range of doses of Myoview given at one time to subjects/patients is from 5.6 to 48.7 mCi. Proposed doses for labeling and marketing are 5-8 mCi for rest, 15-24 mCi. for exercise or pharmacologic stress.

10:3:1 Single Stress Agent Studies PR98-301, PR95-302, P53-006, PR 94-304 (Source: SAS tabulations, pp. 1431-1433, vol. 6)

Of the 438 patients with known or suspected CAD enrolled in the single-pharmacologic stress agent studies, 423 were evaluable. The reasons for the 15-subject discrepancy are as follows: one subject did not have dosing data recorded, 10 underwent exercise stress, 3 had no documentation as to whether they had exercise or pharmacologic stress, and 1 had a dose of Myoview infiltrated (p. 1357 of submission). A total of 317 subjects received adenosine, 94 dipyridamole and 14 dobutamine. In Study #PR94-304, 51 subjects received a single dose of Tl-201 at rest, and 26 in Study # PR95-302 received Tl-201 during stress. With respect to aminophylline, given to counteract the effects of dipyridamole, documentation is provided for only 2

of the 4 studies (PR95-302 and P53-006); 64 of 90 patients receiving Myoview and dipyridamole were given aminophylline (71%). The mean doses of Myoview for the 4 single-stress agent studies ranged from 22.12 to 33.79 mCi for stress and from 7.46 to 7.79 mCi for rest. For Study #PR94-304, a predetermined dose of 25.0 mCi was given to all 60 subjects.

Reviewer's comment: Documentation is needed as to whether aminophylline was given prophylactically or to counter a reaction to dipyridamole, for all studies in the safety database.

10:4:2 Multiple Stress Agent Study PR96-301 (Source: SAS tabulations, pp.1434, vol. 6)

Of the 49 subjects (8 healthy subjects and 41 CAD patients) enrolled in the multi-agent study, 48 received a dose of Myoview with exercise, 39 with adenosine, 39 with dipyridamole and 38 with dobutamine. Ten subjects (1 healthy, 9 with CAD) withdrew after exercise without under-going pharmacologic stress. All who were to receive dipyridamole were given prophylactic aminophylline to reverse the pharmacologic effects of dipyridamole. The doses of Myoview ranged from [illegible] to [illegible] mCi across all stress agents, with a mean dose for rest: 28.03 mCi; for exercise: 28.11 mCi; for dipyridamole: 29.01 mCi; for adenosine: 29.34 mCi and for dobutamine: 29.04 mCi. Thirty-eight patients received a total of 4 doses of Myoview.

10:4:3: Literature Studies (Source: Vol. 7, pp. 1397-1402)

A total of 603 patients were given Myoview in the seven studies submitted by the sponsor in support of efficacy: 65 patients underwent stress with adenosine triphosphate, 92 with adenosine, 149 with dipyridamole and 297 with dobutamine. Doses of Myoview ranged from 5 mCi to 20 mCi, with a maximum of 30 mCi in 1 day and 60 mCi over 3 days.

10:5 Adverse Events (AE's) (Summarized in Table #30)

10:5:1 Single Stress Agent Studies PR98-301, PR95-302, P53-006, PR 94-304 (Source: SAS tabulations, pp. 1435-1476, 1485-1555, vol. 6)

Of the 438 patients in the single-stress agent studies, 319 experienced at least one AE (73%) for a total of 742 events. These are summarized in a table reproduced from the sponsor (Table #30 on next page, from Table #9.1.2.2, page 1381-2, vol. 6 of submission) where all AE's occurring in $\geq$1% of the population are classified by type for each study and the 4 studies combined. The events are then broken down by pharmacologic stress agent, and compared with frequency rates noted in the package insert for the respective stress agent. The AE's were then broken down for each study by relationship to the administration of Myoview or the respective stress agent.

There were no deaths, serious AE's or patient withdrawals due to adverse events in the four single-agent trials.

The most frequent AE's reported for the single-agent studies were angina: 171 patients (39%), flushing: 156 patients (36%) and dyspnea: 121 patients (28%). Two patients undergoing adenosine stress in Study PR98-301

experienced five AE's which the sponsor considered related to Myoview injection; there were 2 episodes of flushing and 1 each of angina, abdominal pain and abnormal vision.

Reviewer's comments: 1) A narrative description of the AE's considered related to Myoview should be in the ISS discussion.

2) Since the sponsor did not do a separate comparison of AE's with Myoview alone vs. Myoview plus stress agent, it is not possible to determine to which drug to attribute the events. The sponsor is only able to say that the adverse event profile of the Myoview/stress agent combination is similar to the AE profile described in the package insert for the respective stress agent.

10:5:2 Multiple Stress Agent Study PR96-301 (Source: SAS tabulations, pp. 1477-1484, 1556-1562, vol. 6)

Of the 49 patients in the multi-stress agent study, 44 experienced at least one AE (90%), for a total of 170 events. These are summarized in a table from the sponsor (page 1393, vol. 6 of submission) where events occurring in ≥ 5% of subjects are classified by type. The events are then broken down by pharmacologic stress agent and exercise, and compared with frequency rates noted in the package insert for the respective stress agent. Review of the table and related SAS tabulations of adverse events indicates that AE rates with Myoview closely correspond to the expected rates for each stress agent.

There were no deaths. Two patients were withdrawn due to serious AE's in this multi-agent trial. One experienced ventricular tachycardia and dyspnea, which was attributed to exercise and spontaneously resolved. The other experienced ST segment deviations (not described) and angina during exercise which completely resolved after sublingual nitroglycerin in approximately 30 minutes, similar to a response he experienced on two prior exercise tests.

The most frequent AE's reported for this study were angina in 23 patients (47%), flushing in 23 patients (47%) and headache in 20 patients (40%). None of the AE's were attributed to Myoview by the sponsor. The occurrence of AE's was greatest with adenosine: 38/39 (97%), then dobutamine: 31/38 (82%) then dipyridamole: 27/39 (69%), and finally exercise: 17/49 (35%). Again, the incidence and type of AE's experienced during pharmacologic stress reflect reports in the literature and the package insert for the respective FDA-approved stress agents.

TABLE #31: ADVERSE EVENTS (for sponsor's single-stress agent trials; reproduced on next page from Table #9.1.2.2, pp. 1381-2, vol. 6)

TABLE #32: ADVERSE EVENTS (for sponsor's multi-stress agent trial; reproduced on page 55 from Table #9.2.2.2, p. 1393, vol. 6)

Table 9.1.2.2
Summary of Tc-99m Tetrofosmin Subjects with Adverse Events [a] by Type for Each Single-stress Agent Study and Combined (Events Occurring in >1% of Subjects)

	Number (%) of Te-99m Tetrofosmin Subjects				
	PR98-301 [b]	PR94.304 [c]	PR95-302 [d]	P53-006 [e]	Combined
Adverse Event	(N=284)	(N=64)	(N-26)	(N=64)	(N=438)
Any event	**240 (85)**	**16 (25)**	**20 (77)**	**43 (67)**	**319 (73)**
Angina pectoris	125 (44)	8 (13)	11 (42)	27 (42)	171 (39)
Flushing	139 (49)	3 (5)	4 (15)	10 (16)	156 (36)
Dyspnea	109 (38)	8 (13)	0 (0)	4 (6)	12 (28)
Headache	31 (11)	4 (6)	9 (35)	19 (30)	63 (14)
Abdominal pain	41 (14)	2 (3)	0 (0)	3 (5)	46 (11)
Dizziness	23 (8)	0 (0)	2 (8)	5 (8)	30 (7)
Anxiety	11 (4)	0 (0)	0 (0)	0 (0)	11 (3)
Palpitation	9 (3)	0 (0)	0 (0)	0 (0)	9 (2)
Hypotension	5 (2)	0 (0)	0 (0)	0 (0	5 (1)
Nausea	0 (0)	2 (3)	1 (4)	5 (8)	8 (2)
Pain	4 (1)	0 (0)	0 (0)	1 (2)	5 (1)
Paresthesia	5 (2)	0 (0)	0 (0)	0 (0)	5 (1)
Hot flushes	3 (1)	0 (0)	0 (0)	1 (2)	4 (0.9)
Sweating increased	4 (1)	0 (0)	0 (0)	0 (0)	4 (0.9)
Taste perversion	4 (1)	0 (0)	0 (0)	0 (0)	4 (0.9)
Coughing	3 (1)	0 (0)	0 (0)	0 (0)	3 (0.7)
Arrhythmia	0 (0)	0 (0)	0 (0)	2 (3)	2 (0.5)
Asthenia	1 (0.4)	0 (0)	0 (0)	1 (2)	2 (0.5)
Bronchospasm	1 (0.4)	0 (0)	0 (0)	1 (2)	2 (0.5)
ECG abnormal (specific)	0 (0)	0 (0)	0 (0)	2 (3)	2 (0.5)
Fatigue	1 (0.4)	1 (2)	0 (0)	1 (2)	3 (0.7)
Hypoesthesia	0 (0)	1 (2)	1 (4)	1 (2)	3 (0.7)
Depersonalization	0 (0)	0 (0)	1 (4)	0 (0)	1 (0.2)
Ear disorder, NOS	0 (0)	0 (0)	1 (4)	0 (0)	1 (0.2)
Hypertension	0 (0)	1 (2)	0 (0)	0 (0)	1 (0.2)
Mouth dry	0 (0)	0 (0)	0 (0)	1 (2)	1 (0.2)
Vomiting	0 (0)	0 (0)	0 (0)	1 (2)	1 (0.2)

a Subjects may have reported more than one adverse event type. All adverse events are listed by their WHO preferred term.

b Subjects were stressed with adenosine or dobutamine, at the discretion of the investigator.

c Includes all subjects in the study (exercise stress and pharmacologic stress)..Pharmacologic stress included dipyridamole, adenosine or dobutamine, at the discretion of the investigator, in subjects unable to exercise.

d Signs and symptoms related to dipyridamole administration.

e Includes adverse events and signs and symptoms related to dipyridamole administration.

Table 9.2.2.2
Summary of Subjects with Adverse Events [a] by Stress Agent for PR96-301

(Events Occurring in >5% of Subjects)
Number (%) of Te-99m Tetrofosmin Subjects

	EXERCISE	ADENOSINE	DIPYRIDAMOLE	DOBUTAMINE	Combined
Adverse Event	(N=49)	(N=39)	(N-39)	(N=38)	(N=49)
Any event	**17 (35)**	**38 (97)**	**27 (69)**	**31 (82)**	**44 (90)**
Angina pectoris	5 (10)	18 (46)	7 (18)	10 (26)	23 (47)
Flushing	0 (0)	20 (51)	6 (15)	4 (11)	23 (47)
Headache	0 (0)	9 (23)	15 (38)	3 (8)	20 (41)
Palpitation	0 (0)	2 (5)	0 (0)	11 (29)	13 (27)
Dyspnea	6 (12)	6 (15)	1 (3)	2 (5)	12 (24)
Leg Pain	5 (10)	0 (0)	1 (3)	0 (0)	6 (12)
Paresthesia	0 (0)	4 (10)	0 (0)	1 (3)	5 (10)
Dizziness	1 (2)	2 (5)	4 (10)	0 (0)	4 (8)
Arrhythmia (ventricular)	2 (4)	0 (0)	0 (0)	1 (3)	3 (6)
Arrhythmia	0 (0)	0 (0)	0 (0)	2 (5)	2 (4)
Nausea	0 (0)	2 (5)	0 (0)	1 (3)	2 (4)
Pain	0 (0)	0 (0)	2 (5)	0 (0)	2 (4)

a Subjects may have reported more than one adverse event type. All adverse events are listed by their WHO preferred term.

Reviewer's comment: A narrative description of the serious AE's should have been included in the ISS discussion.

10:5:3 Adverse Events Reported in Literature Studies

The most common adverse events were chest pain and ischemic ECG changes; all were reversible. Changes in vital signs were those expected with the administration of the respective stress agents.

For dipyridamole, AE's were only reported by Fukuzawa: 7/54 had chest pain (13.5%) and 4/54 headaches (7.8%). No adverse events associated with Myoview were reported.

For adenosine, results are reported for Cuocolo 1996 and 1997 as well as Mahmood 1995. No adverse events associated with Tc-99m tetrofosmin were reported. Chest pain was the most common AE, followed by flushing, headache and lightheadedness, all reported in the package insert or literature for adenosine.

For adenosine triphosphate, no adverse events associated with Myoview were reported.

For dobutamine, in the study by Thorley (1995), two adverse events were attributed to Myoview: nausea and vomiting for about 1 hour and a metallic taste about 12 hours after Myoview injection. No other AE's attributed to Myoview were reported.

10:5:4 Spontaneous Adverse Event Reports

Since the marketing of Myoview in Feb. 1996 for myocardial perfusion imaging, two AE's have been reported as being possibly related to Myoview. These were reported in patients who underwent adenosine stress (one in the US and one in Belgium), though the sponsor is not sure if the second patient received Myoview. Both involved skin and edema; the first patient had swollen lips, thirst and blistering of the hands; the second a papular rash and erythema. The first responded quickly to Benadryl; the second was given cortisone, but the response was not described.

10:6 Vital Signs (Systolic, diastolic BP, pulse) The sponsor's criteria for a significant change are as follows: blood pressure change of >20 mm Hg or a change in pulse of >15 bpm (p. 1372, vol. 5)

10:6:1 Single Stress Agent Studies PR98-301, PR95-302, P53-006 (PR 94-304 did not include vital signs) (SAS tabulations, pp. 1563-1576, vol. 6)

Among the 374 patients receiving Myoview in the three studies above, the mean increase in maximum heart rate was 16.8 bpm; maximum systolic blood pressure (BP) was 7.1 mm Hg, and diastolic BP was −1.5 mm Hg. For the 26 patients receiving Tl-201, corresponding values were 6.8mm, -1.5 mm and 15.5 bpm. For maximum systolic BP, 17.0% (63/371) given Myoview experienced a change of > 20 mm Hg, while for Tl-201, 11.5% (3/26) had a change of >20 mm Hg. For minimal diastolic BP, 0% (0/371) given Myoview had a change of >20 mm Hg, while for the 26 given Tl-201, the changes in minimal diastolic BP were not given. For maximal heart rate, 50.8% (190/374) given Myoview had a change of >15 bpm, while 50% (13/26) given Tl-201 had a change of >15 bpm. In general, the changes in vital signs in those subjects receiving Myoview and thallium reflected the particular stress agent given, with dobutamine producing the greatest mean increases in heart rate and systolic pressure; understandable given its nature as a catecholamine.

Reviewer's comment: Values for minimum systolic and diastolic blood pressure were not given for Tl-201 patients, as well as 95 patients receiving Myoview.

10:6:2 Multiple Stress Agent Study PR96-301 (source: SAS tabulations, pp. 1577-1589, vol. 6)

Among the 48 patients receiving Myoview in the multi-stress agent study, the mean increase in maximum heart rate after exercise was 79.6 bpm, after dobutamine 62.5 bpm, after dipyridamole 17.5 bpm, and adenosine 21.0 bpm. The mean increase in maximum systolic blood pressure (BP) was 30.4mm Hg for exercise, 24.2 mm Hg for dobutamine, -0.1 mm Hg for dipyridamole and −2.0 mm Hg for

adenosine. For maximum diastolic BP, corresponding changes for exercise, dobutamine, dipyridamole and adenosine were 3.5, -3.5, -0.8 and -3.4 mm Hg, respectively.

For maximal heart rate, 100% (48/48) given Myoview changed >15 bpm with exercise, 97.4% (37/38) with dobutamine, 56.4% (33/39) with dipyridamole and 66.7% (26/39) with adenosine. For maximum systolic BP, 70.1% (34/48) given Myoview changed >20 mm Hg with exercise, 55.3% (21/38) with dobutamine, 5.1% (2/39) with dipyridamole and 2.6% (1/39) with adenosine. For maximum diastolic BP, 0% (0/46) given Myoview changed >20 mm Hg with exercise, dobutamine, dipyridamole or adenosine. Figures for minimum diastolic BP were not given. Again, the changes in vital signs seen in those subjects receiving Myoview reflected the particular stress agent given, with dobutamine and exercise producing the greatest mean increases in BP and heart rate; understandable given this drug's nature as a catecholamine. (SAS tabulations, pp. 1577-79, vol. 6)

10:6:3 Studies from the Literature

For dipyridamole, the heart rate rose and systolic pressure fell slightly with dipyridamole infusion. Diastolic BP was not recorded. Vital signs obtained with Myoview and adenosine also reflected the hemodynamic profile of adenosine: heart rate typically rose while both systolic and diastolic BP fell slightly.

10:7 Electrocardiograms (QT or QTc intervals not reported; ST segment deviations of ≥1mm are considered by the sponsor to represent ischemia).

10:7:1 Single Stress Agent Studies PR98-301, PR95-302, P53-006, (PR 94-304 did not include ECG's) (Source: SAS tabulations: pp. 1590-1597, vol. 6)

ECG results were presented for the 3 studies above separately; data was not pooled. Data from SAS tables were combined for the purpose of analyzing ST-segment changes by this reviewer: Of 374 patients overall, 284 experienced ST deviations of <1mm, 27 of 1 to 2 mm, and 4 of >2mm. Missing is data from 63 patients. In study #PR95-302 no significant differences in ST-segment deviation were seen between those given Tl-201 and Myoview. In study #PR98-301, the most frequent ECG responses to pharmacologic (adenosine) stress were arrhythmia in 21/284 (7%) and second-degree A-V block in 13/284 (5%). ECG response data is missing for 8/284 (3%). (table, page 1390, vol. 6)

10:7:2 Multiple Stress Agent Study PR96-301 (Source: SAS tabulations: pp. 1598, vol. 6)

Of 49 patients overall, 23 had normal and 26 abnormal ECG's at baseline. ST-segment changes were not evaluated with exercise. With dobutamine, 14/38 (37%) experienced ST deviations of <1mm, 6/38 (15.8%) of 1 to 2 mm, and 2/38 (5.3%) of >2mm. With dipyridamole, 1/39 (2.6%) experienced ST deviations of <1mm, 2/39 (5.2%) of 1 to 2 mm, and 0/39 (0 %) of >2mm. With adenosine, 3/39 (7.7%) experienced ST deviations of <1mm, 2/39 (5.2%) of 1 to 2 mm, and 0/39 (0%) of >2mm. Adding the above figures, ST changes representing ischemia (>1mm) were seen in 21% of those receiving dobutamine, 5% of those receiving dipyridamole and 5% receiving adenosine. Missing is data from 2 patients given adenosine.

10:7:3 Studies from the Literature

For dipyridamole, 6/54 patients developed ST-T changes suggestive of ischemia (11%). For adenosine, ECG changes reported were ST-T changes associated with stress-induced ischemia.

10:8 Additional Safety Data

10:8:1 Non-IND Studies

Three foreign studies not conducted under IND[——] were reported in the ISS. In Study #P53-006C, 16 subjects underwent dipyridamole/Myoview imaging. 10 experienced headaches, 9 chest pain, 4 dizziness and 3 diffuse weakness. Labs were abnormal in 3 subjects: 1 increased bilirubin and 2 increased LDH. In Study #P53-007, 60 subjects (47 with CAD) underwent Myoview/ dobutamine SPECT imaging. One patient developed unstable angina 2 days after Myoview/dobutamine testing (a serious AE), not attributed to Myoview, but possibly dobutamine. Two events (chest pain and bigeminy on ECG) were considered possibly related to Myoview, but the first spontaneously resolved and the second resolved upon discontinuing dobutamine. In Study #P53-016, 5 deaths which investigators had not attributed to Myoview occurred among the 60 patients enrolled. All were blamed on the underlying CAD disease process; three were peri-operative. As study reports and original protocols were not available, these data are considered testimonial.

10:8:2 Arbutamine Study (Arbutamine is FDA-approved for stress)

A fourth foreign non-IND trial in approx. 1000 patients involved arbutamine, an analog of dobutamine. Five patients were given Myoview at the time of arbutamine stress. The stress agent was administered via a computerized drug delivery device based on heart rate ——————. Two subjects developed ischemic ECG changes; one with a history of CHF experienced dyspnea.

10:8:3 Non-ISE Literature Articles

Two articles in addition to those in the ISE involved a total of 84 subjects undergoing myocardial perfusion imaging with both Tc-99m sestamibi and/or tetrofosmin. Flamen's study (1995) enrolled 30 patients given dipyridamole as a stress agent; on 2 separate days, Tc-99m sestamibi and tetrofosmin were given. Senior's study (1995) enrolled 54 to undergo dobutamine stress; patients were given Myoview (27 pts.) or sestamibi (27 pts.), along with stress echocardiography, in a one-day protocol. No patients in either study experienced an AE associated with either myocardial perfusion imaging agent.

10:9 Overall Safety Summary and Comments

Review of the safety database used for the ISS, efficacy studies in the ISE which contained safety data, and additional literature/foreign data in the submission and the supplementary safety data volume SEI 003 sent to the Division on 7/23/99 suggests Myoview to be safe if used in conjunction with approved pharmacologic stress agents. The adverse events, vital sign and ECG changes reported appear to reflect the stress agents used, and do not represent a significant change from those reported in the literature or the package inserts for the respective approved stress agents. However, the absence of AE monitoring after resting Myoview injections renders it impossible to determine whether an AE is related to administration of Myoview or the respective pharmacologic stress agent. This is a limitation, however, it is largely overcome by the safety profile of Myoview accumulated up to this point in time.

11: Labeling Review and Recommendations:
(if and when ultimately approved)

(References are made to the Draft Labeling, vol. 1, Application Summary, pp. 13-16). No annotation was provided.

11:1 Description: No changes recommended.
11:2 Clinical Pharmacology: No changes recommended.
11:3 Clinical Trials:
The table already in this section should be designated Table #1.

The first insert box on page 010 (vol. 1) should read:

DRAFT

11:4 Indications and Usage: No changes recommended.
11:5 Contraindications: No changes recommended.
11:6 Warnings: No changes recommended.

DRAFT

11:10 Radiation Dosimetry: No changes recommended.
11:11 Instructions for the Preparation of Tc-99m Tetrofosmin Injection: No changes recommended.
11:12 How Supplied: No changes recommended.
11:13 Storage: No changes recommended.

12: Conclusions:

12:1 Sponsor's Conclusions

12:1:1 Efficacy: (Taken from p. 1688-1690, vol. 7 of submission)

"In summary, Tc-99m tetrofosmin is efficacious at the currently approved dose as a myocardial perfusion imaging agent whose uptake in the myocardium is related to myocardial blood flow and myocardial viability. It allows imaging of myocardial perfusion, and enables detection of perfusion abnormalities, regardless of the mechanism (exercise or pharmacologic stress) which is used to provoke those perfusion abnormalities."

12:1:2 Safety: (Taken from p. 1417, vol. 6 of submission)

"Intravenous administration of MYOVIEW under pharmacologic stress and resting conditions to subjects undergoing myocardial perfusion imaging was found to be safe and well-tolerated at doses routinely used for clinical myocardial perfusion imaging. There were no serious adverse events associated with MYOVIEW nor were there significant trends or individual changes in any safety parameter".

"Overall, the frequency and types of adverse events seen with the three pharmacologic stress agents (adenosine, dipyridamole and dobutamine) used in these studies were generally similar to those note in the package insert and in the literature for the respective agents. As expected, changes in heart rate and systolic blood pressure were less pronounced with the vasodilator pharmacologic stress agents adenosine and dipyridamole compared with the catecholamine pharmacologic stress agent dobutamine."

12:2 Reviewer's Conclusions

12:2:1 Sponsor's Clinical Trials: Efficacy

Efficacy results from the two pivotal trials suggest that Myoview may be useful in the evaluation of suspected coronary artery disease, though support for the new expanded indication could be stronger. The combined sample size of 84 is small, but appears to be adequate to support the claim. The two studies are of different design and endpoints, though both studies incorporated coronary angiography as a truth standard. Nevertheless, the use of consensus interpretation of images by the blinded readers is a matter of concern, as independent reads are recommended in the Draft Guidance. Poor sensitivities for Myoview in certain vessel territories (LAD and LCx) raise a concern that some stenoses may be missed if Myoview is used as a screening test for CAD in the setting of pharmacologic stress. This is especially true in patients with 3-vessel disease, which may result in "balanced", and thus undetectable, myocardial ischemia. This problem exists with other approved perfusion agents (Tl-201 and Tc-99m sestamibi), however, and the use of Myoview as a screening test was not specified in the proposed labeling. Poor specificity results in these studies most

likely reflects pre-test selection bias and post-test referral bias, resulting in a high prevalence of CAD in the subjects studied. This has been acknowledged by the sponsor (p. 1688, vol. 7). Though these trials would probably be insufficient as support for a new NDA, the studies appear adequate to support the expanded indications for Myoview as a drug already on the market with an approved exercise stress indication.

12:2:2 Literature Trials: Efficacy

The medical literature was unable to provide support for the dipyridamole/Myoview imaging indication, for reasons explained in Section #8:1. The two articles by Cuocolo et. al provided the support for adenosine/Myoview imaging.

The Cuocolo 1996 and 1997 studies do have inherent design flaws of their own (small sample sizes, and selection bias toward documented CAD patients, for example). They have, however, the advantages of direct comparison of exercise and adenosine Myoview SPECT images acquired under otherwise identical conditions, prospective and consecutive subject enrollment, and a detailed description of dosing, acquisition and processing procedures. Both studies compared Tc-99m tetrofosmin SPECT to coronary angiograms as a truth standard. Efficacy was evaluated on a subject-by-subject, vessel-by-vessel and segment-by-segment basis. Importantly, readers of the SPECT images were blinded to angio results, but they did reach a consensus interpreting the scans. As with the sponsor's trials, the use of consensus interpretation of images is a matter of concern. Though 7 subjects participated in both trials, reducing the total number to 60, the combined sample appears to have sufficient size to be supportive. Despite the shortcomings mentioned above, results for detecting CAD are on a par with pharmacologic stress studies using Tl-201 and other Tc-99m myocardial perfusion agents.

Data from studies using Myoview and dobutamine cannot be used as support as FDA has not yet approved dobutamine for pharmacologic stress.

In summary, the two articles by Cuocolo et. al. do help support adenosine/Myoview imaging as proposed for detection of regions of reduced myocardial perfusion in patients unable to exercise adequately.

12:2:3 Efficacy: Reviewer's Conclusion

Studies P53-006 and PR95-302 for dipyridamole, the two articles by Cuocolo et. al for adenosine, prior experience with exercise/Myoview studies and the similarity of exercise and pharmacologic stress using other myocardial perfusion agents point to a recommendation for approvability of this supplemental application for the expanded indication. Ultimate approval for Myoview with

pharmacologic stress should be contingent on the ability of the sponsor to demonstrate efficacy after independent blinded re-reading of images in the two pivotal studies P53-006 and PR95-302.

12:2:4 Safety:

Safety data was submitted in 5 studies by the sponsor. Four studies used a single stress agent in 438 subjects; one study used all three stress agents and treadmill exercise in each of 49 subjects. Review of this safety database, along with additional data from the literature and non-IND studies, suggest Myoview to be safe if used with pharmacologic stress. Adverse events, vital signs and ECG changes reported appear to reflect those reported in the package inserts of the stress agent(s) used.

13: Recommendations:

13:1 Overall approvability: APPROVABLE (AE)

13:2 Recommended changes in the labeling (if ultimately approved):
Listed in Section #11.

13:3 Recommended further clinical investigations:

A blinded re-reading of the images in both of the sponsor's pivotal trials, P53-006 and PR95-302, with independent interpretations by each blinded reader, is recommended. Ultimate approval of the application would depend on the ability of this re-read to demonstrate adequate sensitivity and specificity of pharmacologic stress Myoview imaging as compared to coronary angiography as a standard of truth. If the data following the re-read is not sufficiently robust, the sponsor may need to conduct a new study, perhaps comparing Myoview with an approved Tc-99m perfusion agent (i.e. Tc-99m sestamibi) in the setting of pharmacologic stress.

14: Signature Section:

14:1 /S/ 12/8/99
Nelson B. Arnstein, M.D. Date
Medical Reviewer

14:2 /S/ MD See Clinical Team Leader Memo 12/20/99
Sally Loewke, M.D. Date
Clinical Team Leader, HFD-160

14:3 /S/ I have reviewed Division Director Memo dated 12/20/99. 12/20/99
Patricia Y. Love, M.D. Date
Division Director, HFD-160

15: C.C. list:

HFD-160 NDA File
HFD-160 Division File
Division Director: Patricia Y. Love, M.D.
Project Manager: Patricia Stewart, CSO
Medical Officer: Nelson B. Arnstein, M.D.
Clinical Team Leader: Sally Loewke, M.D.
Statistics: Anthony Mucci, Ph.D.

APPENDIX 1: CLINICAL REVIEW OF STUDY sNDA #20,372
#PR94-304 (Study Report #2951) Volume 4, pp. 743-875

This document contains a review of Phase 3 Study #PR94-304: Use of Technetium-99m Tetrofosmin for Myocardial Perfusion Imaging". This study was conducted by the sponsor to evaluate the efficacy of a dual-isotope SPECT myocardial perfusion imaging protocol combining Myoview and Thallium-201 in the setting of exercise and pharmacologic stress.

1) STUDY OBJECTIVE: (quoted from sponsor) This Phase 3 study was conducted "to evaluate the use of a rest thallium-201/stress (exercise or pharmacologic) technetium-99m tetrofosmin single-photon emission computerized tomography (SPECT) imaging protocol in the assessment of myocardial perfusion. To evaluate safety, adverse events were also monitored."

2) STUDY DESIGN: GENERAL

This study is of the open-label, single-center non-randomized single-administration type, without placebo. Tc-99m tetrofosmin (Myoview) SPECT myocardial perfusion images obtained after exercise or pharmacologic stress (adenosine, dipyridamole or dobutamine) were combined with thallium-201 rest images. Scintigrams were not interpreted by blinded readers, nor were they compared to a truth standard. Safety was assessed through monitoring of adverse events; vital signs and ECG's were not recorded.

3) PATIENT POPULATION

The original protocol #PR94-304 called for enrollment of approximately 250 patients in one institution; 64 patients actually enrolled of whom 51 were evaluable for safety and 50 for efficacy. [redacted] after 64 subjects was [redacted] from the study center. The subjects' age was to be ≥18 years. The protocol called for entry of subjects meeting inclusion/exclusion criteria, with an indication for myocardial perfusion imaging. A subject was to be removed from the study if they developed any adverse events; he/she would be replaced.

4) INCLUSION AND EXCLUSION CRITERIA

E) Inclusion criteria

5) Adult patients 18 years of age or older.
6) Subjects must have been referred for myocardial perfusion imaging.
7) Subjects must give written informed consent.

B) Exclusion criteria

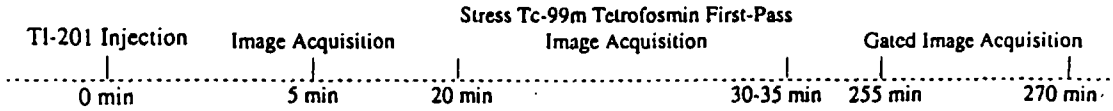
14) Subject has used experimental drugs within 30 days of study.
15) Subject has had prior CABG surgery.
16) Subjects with acute myocardial infarction.
17) Female subject who is pregnant, lactating or of childbearing potential without confirmation of absence of pregnancy.

5) STUDY DESIGN: TIMETABLE: No study timetable was provided.

6) DOSAGES AND ADMINISTRATION:

The exercise/pharmacologic stress protocols for thallium-201 and Tc-99m tetrofosmin are portrayed in Fig #1 below. (p. 754 of submission).

Figure 1
Time Scale of Combined Test Thallium-201 and Tc-99m Tetrofosmin/Pharmacologic or Exercise Stress Protocol



Thallium-201 was to be given as a 3 mCi dose, followed by SPECT imaging acquisition, begun 5 minutes later for the resting images.

Exercise was to be symptom-limited, on a treadmill. Specific exercise protocols were not given. Stress testing was begun 20 minutes after Tl-201 imaging, at the conclusion of rest imaging.

Pharmacologic stress: Dipyridamole, adenosine or dobutamine were to be used at the discretion of the investigator if the patient was unable to exercise. Details pertaining to the use of these drugs were not given.

Myoview was to be given as one bolus dose, 25 mCi, at peak stress. This dose was fixed to allow for planed quantitative analysis of myocardial counts. The subject, drug administrator, safety monitors and staff were not blinded with respect to the study drug given (open-label).

7) SPECT IMAGE ACQUISITION: SPECT mages were to be acquired 5 minutes after Tl-201 injection for rest images. If a resting defect was seen, late redistribution Tl-201 images were to be acquired if clinically indicated (time not specified). For Myoview, imaging was started immediately after the peak stress injection for first-pass images, and 10-15 minutes later for gated equilibrium images. Particulars of the gamma camera, collimators, acquisition parameters and reconstruction algorithms were not given.

Reviewer's comment: Although delayed gated image acquisition (255-270 minutes) is indicated in Figure #1, it is not described in the protocol. It is not clear from the submission if a 10-15 min. or 4 hour gated acquisition was done.

8) IMAGE INTERPRETATION AND EVALUATION: SPECT Tl-201 images were to be read as reversible, non-reversible or mixed, and Tc-99m tetrofosmin images as absent or present defects. Quality of the images was to be rated as excellent, good, fair, acceptable or unacceptable. Quantitative measurements would be made of total myocardial counts, target-to-background ratios and defect contrast.

9) CORRELATIVE IMAGING: Coronary angiography was to be done only if clinically indicated.

10) SAFETY EVALUATIONS

A) Pre-study baseline:

Subjects were to be given a complete history and physical examination, informed consent obtained and inclusion/exclusion criteria checked prior to study participation.

B) Post-procedure:

1) Study Dropouts and Withdrawals: Patients were to be free to drop out at any time. Subjects were asked to withdraw if they experience any adverse events. A complete final examination was performed at the time of withdrawal. If withdrawal occurred after Myoview injection, the reason was recorded in the CRF.

2) Adverse Events: Monitoring for AE's was to be carried out throughout the imaging procedure. To be recorded were a description of the event, date and time of onset and resolution, serious vs. nonserious, and possibility of relationship to Myoview administration. Serious or unexpected AE's were to be reported to the sponsor immediately and a report submitted within 10 working days of its occurrence (3 days for fatal or life-threatening AE's).

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

11) STATISTICAL METHODS

Adverse event and efficacy data were to be tabulated and listed, but formal statistical analyses were not planned. Diagnostic accuracy of the Tl-201/ Myoview studies was to be analyzed by computation of sensitivity and specificity among those undergoing coronary angiography, and normalcy rate of subjects with a pre-test likelihood of CAD.

12) STUDY RESULTS

A) Demographics and Baseline Characteristics

The protocol called for enrollment of approx. 250 patients at one institution; the study was stopped after 64 patients were ultimately enrolled. The reason for early termination was that the principal investigator left the institution at which the study was being conducted. Of these, 63 were dosed with Tl-201 and Myoview; ten underwent exercise stress. For three subjects, the stress procedure was not specified. Fifty patients underwent pharmacologic stress dual-isotope SPECT imaging. Four of these were subsequently lost to followup, though efficacy and safety data were available. Table #1 on the next page summarizes the demographic information for the 64 patients in Study #P94-304.

TABLE #1: DEMOGRAPHIC CHARACTERISTICS (From Table #10.3, p. 761)

Characteristic	N = 64
Age: Mean	68.46 years
SD	13.54
Range	27.7-91.2
Race: White	57 (89%)
Black	2 (3%)
Asian/Oriental	2 (3%)
Other	3 (5%)
Gender: Male	27 (42%)
Female	37 (58%)

C) Protocol Deviations (p.760 of submission) Most deviations from the protocol as written involved SPECT image acquisition outside the specified window after injection of the tracer. For Tl-201, 24/51 subjects were injected outside of 5 minutes post-injection; for Myoview, 48/50 subjects were injected outside 10-15 min. post-injection (12 at >46 minutes). One subject was not scanned due to infiltration of the Myoview dose.

D) Dosage and Administration (from p. 761 of submission)

All 64 subjects were given one dose of Tl-201, while 63 were given Myoview. One dose of Myoview was infiltrated (see above). Ten underwent exercise stress; 46 received adenosine, 4 dipyridamole and 1 dobutamine. For 3 subjects, the type of stress was not recorded.

Reviewer's comment: Due to the early termination of the study, less than 25% of the intended population actually enrolled, and <20% were evaluable for efficacy. Only 9 underwent coronary angio-grams; sensitivity and specificity could not be determined. The normalcy rate was not calculated as "pre-test likelihood of CAD" was never defined. Even more significant to the study's primary focus, quantitative analysis of the images (contrast, myocardial counts, target-to-background ratios) were not evaluated "because the CRF was not specifically designed to capture the necessary data" (p. 759). All in all, this does not leave much data on which to make an efficacy assessment of Tl-201/Myoview dual-isotope SPECT in the setting of pharmacologic stress.

E) Safety Results: Adverse Events:

There were no serious adverse events. According to the table below, 11 of the 51 evaluable patients receiving Myoview (22%) experienced a total of 25 adverse events in this phase 3 trial. According to the sponsor, no apparent relationship was seen between the administration of Myoview and frequency of adverse events. Dyspnea, angina pectoris, and headache were the most common AE's (12%, 10% and 8% of the subjects, respectively). According to the investigator, AE's were most likely attributed to adenosine, as 46 of the 51 subjects were given this drug.

Four deaths were reported during the followup period (length not specified, but death occurred over 3 months after imaging in all cases). The cause was reported in 2 cases: pneumonia and metastatic cancer).

TABLE #2: NUMBER OF PATIENTS WITH ADVERSE EVENTS
(from Table #12.2.2, p. 766 of submission)

Table 12.2.2
Summary of Subjects with Adverse Events by Type [a]

Adverse Event	Number (%) of Subjects			
	Adenosine (N=46)	Dipyridamole (N=4)	Dobutamine (N=1)	Combined (N=51)
Any Event	9 (20)	1 (25)	1 (100)	11 (22)
Dyspnea	4 (9)	1 (25)	1 (100)	6 (12)
Angina pectoris	4 (9)	0 (0)	1 (100)	5 (10)
Headache	2 (4)	1 (25)	1 (100)	4 (8)
Flushing	2 (4)	0 (0)	0 (0)	2 (4)
Nausea	1 (2)	0 (0)	1 (100)	2 (4)
Abdominal pain	0 (0)	1 (25)	0 (0)	1 (2)
Fatigue	1 (2)	0 (0)	0 (0)	1 (2)
Hypertension	1 (2)	0 (0)	0 (0)	1 (2)
Hypoesthesia	0 (0)	0 (0)	1 (100)	1 (2)

[a] Subjects may have reported more than one adverse event type. All adverse events are listed by their World Health Organization (WHO) preferred term.

F) Efficacy Results

The evaluation of efficacy in this study addressed only the endpoint of SPECT image quality; this was a subjective, semiquantitative evaluation of the studies by the principal investigator. Due to the lack of quantitative image data in the CRF's, no statistical analysis was done.

TABLE 3: DIAGNOSTIC EFFICACY (from p. 762 of submission)

Image Quality	Thallium-201 (N=50)	Myoview (N=50)
Excellent	40	38
Good	9	9
Fair	-	1
Acceptable	1	-
Not available	-	2

14) SPONSOR'S CONCLUSIONS: (extracted from page 745 of submission)

- "The SPECT image quality for both rest Tl-201 and stress Tc-99m tetrofosmin scans was rated as excellent or good for 98% and 94% of the subjects, respectively. No scans were uninterpretable."
- "Tc-99m tetrofosmin was found to be safe and well-tolerated at the dose (25 mCi) used in this study."

15) REVIEWER'S COMMENTS

A) Trial design and protocol execution:

The design of this trial was a single-center, open-label, non-randomized type. Such a design would be appropriate only for a supportive rather than a pivotal trial. The imaging protocol was generally followed, though in a number of cases, imaging was done outside the pre-determined time interval after tracer injection. The most significant change was the loss of nearly 75% of the initially planned enrollment. The resulting sample size was small, even if quantitative efficacy data were available. The sponsor also does not adequately explain the failure to record quantitative scan data on the CRF's. In addition, the study did not utilize blinded reading of SPECT images for primary efficacy assessment. The provision of a study timetable would have made it easier to follow the overall study plan. Specifically, although delayed gated image acquisition (255-270 minutes) is indicated in the sponsor's Time Scale (see p. 2 of this review), this acquisition timing is not described in the protocol. It is not clear from the submission if a 10-15 minute or 4-hour gated acquisition was to be done.

F) 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. Unlike the other sponsor-conducted trials in this sNDA, even vital signs and ECG's were not recorded, a serious omission from the safety database. Also, it was not clear how long patients were to be followed for AE's after injection of Myoview (though the patient data listings mention a 1-year followup exam for cardiovascular events).

C) Efficacy results: A subjective rating of scans as "excellent" to "unacceptable" by the principal investigator is clearly not enough to evaluate the utility of dual-isotope SPECT in the evaluation of suspected CAD in the setting of pharmacologic stress. Without objective interpretation of scans by a blinded reader, or at least recording quantitative data (after all, the dose of Myoview was kept at 25 mCi for this purpose), this study cannot add significantly to the sNDA efficacy database.

D) Reviewer's conclusions:

This study does little to add to the data in support of a pharmacologic stress indication for Myoview. Safety data is limited to an adverse event listing, while efficacy is only assessed through a semiquantitative scale of image quality by the principal investigator. It is unfortunate that what was originally planned in the way of subject enrollment and quantitative SPECT data collection was not actually carried out.

APPENDIX 2: CLINICAL REVIEW OF STUDY sNDA #20,372
#PR98-301 (Study Report #2953) Volume 4, pp. 876-1102

This document contains a review of Phase 3 Study #PR98-301: "Pharmacological Stress with Technetium-99m Tetrofosmin". This study was conducted by the sponsor to evaluate the safety of Myoview in the setting of pharmacologic stress with adenosine and dobutamine.

4) STUDY OBJECTIVES: (quote from sponsor) This Phase 3 study was conducted "to determine the type and incidence of serious adverse events associated with pharmacologic stress (adenosine, dobutamine) testing using technetium-99m tetrofosmin scintigraphy." Secondary objectives included determination of "type and incidence of ECG changes and clinical responses associated with pharmacologic stress testing using technetium-99m tetrofosmin scintigraphy."

5) STUDY DESIGN: GENERAL

This study is a non-IND, Phase 3B open-label, safety-only observational multicenter non-randomized type, without placebo or control group. Patients referred for myocardial perfusion imaging under pharmacologic stress underwent Tc-99m tetrofosmin (Myoview) scintigraphy using adenosine or dobutamine as stress agents. Safety was assessed through monitoring of adverse events, vital signs and ECG's during the imaging procedure, and interviewing the patient 24 hours afterward for adverse events. Aminophylline or atropine was to be used if necessary to counteract the effects of adenosine or dobutamine, respectively.

3) PATIENT POPULATION:

The original protocol #PR98-301 called for enrollment of approximately 100 patients at each of 4 institutions; 284 patients actually enrolled of whom 283 were dosed with Tc-99m tetrofosmin. The protocol called for entry of subjects with an indication for myocardial perfusion imaging.

4) INCLUSION AND EXCLUSION CRITERIA:

No formal entry criteria were specified in the protocol. Patients referred for myocardial perfusion imaging who were unable to exercise adequately and thus were candidates for pharmacologic stress were eligible to participate. Demographic breakdown is summarized in Section #10: Study Results.

5) STUDY DESIGN: TIMETABLE:

The study timetable provided is reproduced below (page 968, vol. 4 of submission).

Event	Baseline	During Stress / Imaging	24 Hours Later
Data Recorded	Demographics Vital Signs	Drug Administration Data Vital Signs ECG Response Clinical Response Adverse Events	Adverse Events

Reviewer's comment: The timetable provided by the sponsor is inadequate to give the reviewer a perspective of the overall trial design and plan.

6) DOSAGES AND ADMINISTRATION:

Pharmacologic stress: Adenosine or dobutamine were to be used at the discretion of the investigator. The standard imaging protocol at each site was to be followed. Aminophylline or atropine (depending on the pharmacologic stressor used) was also given according to each institution's guidelines. These were provided as attachments in the submission.

Myoview was to be given at rest (5-8 mCi) and peak stress (15-24 mCi). The subject, drug administrator, safety monitors and staff were not blinded with respect to the study drug given (open-label).

Thallium-201 was specified in the protocols for [redacted] (p. 977), [redacted] (p. 986) and [redacted] (p. 995). However, the Listings of Demographic and Drug Administration Data (p. 998) do not indicate Tl-201 to have been given.

Reviewer's comment: The protocols for individual centers are different, and do not clearly indicate if rest Myoview or Tl-201 doses are given. The dosing of Myoview was also not consistent from center to center.

7) SPECT IMAGE ACQUISITION AND INTERPRETATION:

Each of the four principal investigators submitted specific imaging protocols for their respective institutions. Since this study was conducted to evaluate safety only, these are not pertinent to this discussion.

8) SAFETY EVALUATIONS

A) Pre-study baseline:

Subjects were to be given a complete history and physical examination and informed consent obtained prior to study participation.

B) During and after perfusion imaging:

1) Adverse Events: Monitoring for AE's was to be carried out throughout the imaging procedure. To be recorded were a description of the event, date and time of onset and resolution, serious vs. nonserious, and possibility of relationship to Myoview or stress agent administration. Information about each AE was recorded in the medical record. At 24 hours after imaging, the patient was again questioned for late-occurring AE's. Serious AE's were to be fully described and documented.

Reviewer's comment: No mention is made of recording each AE in the CRF, just the medical record. The CRF (page 969) only asks for details for serious AE's, not nonserious ones.

2) Vital signs: The CRF called for vital sign (heart rate, systolic blood pressure) measurements for baseline and subsequent measurements during imaging. Changes from baseline of >20 mmHg or >15 bpm were considered significant.

Reviewer's comment: The CRF includes only space to record systolic blood pressure, though diastolic is included in the patient data listings. Only systolic BP was analyzed by pharmacologic stress agent.

3) A 12-lead ECG was to be obtained at baseline and during the stress test according to protocols for each institution. The CRF provide for recording of arrhythmias, AV block, ST-segment deviations in 1 mm increments and space for descriptions of other changes.

Reviewer's comment: The CRF has no provision for recording QT-interval changes on the ECG.

4) Laboratory evaluation: No specific laboratory tests (chemistries, CBC, urinalysis) were mentioned in the protocol or to be recorded in the CRF.

9) STATISTICAL METHODS

Adverse event, vital sign and ECG data were to be tabulated and listed. The mean baseline and maximum/minimum values for heart rate and systolic (not diastolic) BP were to be tested for differences in means using the paired t-test. Analyses of heart rate and systolic BP were also to be made by stress agent. No statistical analysis was to be done for adverse events or ECG changes.

10) STUDY RESULTS

A) Demographics and Baseline Characteristics

The protocol called for enrollment of approximately 100 patients at each of 4 institutions. Of these 400, 284 enrolled, of whom 283 have a record of being dosed with Myoview. Dosing data was missing for this one patient; the sponsor attributes this to a recording error, as other data for this patient was recorded. Table #1 summarizes demographic data for Study #P98-301.

TABLE #1: DEMOGRAPHIC CHARACTERISTICS (From Table #12.2, p. 889)

Characteristic	N = 284
Age: Mean	66.71 years
SD	12.20
Range	27-97 years
Weight: (kg) N	270
Mean	85.19 kg.
SD	23.11
Range	39.5-209.1 kg.
Race: White	191 (67%)
Black	70 (25%)
Asian/Oriental	4 (1%)
Other	18 (6%)
Missing	1 (0.4%)
Gender: Male	138 (49%)
Female	145 (51%)
Missing	1 (0.4%)

B) Safety Results: Adverse Events:

There were no deaths or serious adverse events. According to the table below, 240 of the 284 evaluable patients receiving Myoview (85%) experienced a total of 576 adverse events in this phase 3B trial. According to the sponsor, no apparent relationship was seen between the administration of Myoview and frequency of adverse events. Dyspnea, angina pectoris, and flushing were the most common AE's (38%, 44% and 49% of the subjects, respectively). According to the investigator, AE's were most likely attributed to adenosine, as 271 of the 284 subjects (95%) were given this drug.

TABLE #2: NUMBER OF PATIENTS WITH ADVERSE EVENTS
(reproduced from Table #13.2.1, p. 891 of submission)

Summary of Subjects with Adverse Events by Type [a]
Events Occurring in ≥1% of Subjects
(Combined Across Study Sites)

Adverse Event	Pharmacologic Stress Agent Number (%) of Subjects		
	Adenosine (N=271)	Dobutamine (N=13)	Combined (N=284)
Any Event	229 (85)	11 (85)	240 (85)
Flushing	137 (51)	2 (15)	139 (49)
Angina pectoris	120 (44)	5 (39)	125 (44)
Dyspnea	109 (40)	0 (0)	109 (38)
Abdominal pain	40 (15)	1 (8)	41 (14)
Headache	30 (11)	1 (8)	31 (11)
Dizziness	23 (8)	0 (0)	23 (8)
Anxiety	11 (4)	0 (0)	11 (4)
Palpitation	3 (1)	6 (46)	9 (3)
Hypotension	5 (2)	0 (0)	5 (2)
Leg pain	4 (1)	0 (0)	4 (1)
Pain	3 (1)	1 (8)	4 (1)
Paresthesia	5 (2)	0 (0)	5 (2)
Sweating increased	4 (1)	0 (0)	4 (1)
Taste perversion	4 (1)	0 (0)	4 (1)
Coughing	3 (1)	0 (0)	3 (1)
Hot flushes	3 (1)	0 (0)	3 (1)
Back pain	0 (0)	1 (8)	1 (0.4)

[a] Subjects may have reported more than one adverse event type. All adverse events are listed by their World Health Organization (WHO) preferred term.

REF: Section 15.2.1

TABLE #3: RELATIONSHIP OF ADVERSE EVENTS TO TREATMENT
(reproduced from Table #13.2.2, p. 892 of submission)

Summary of Adverse Events by Relationship to Treatment [a]
(Combined Across Study Sites)

Adverse Event	Pharmacologic Stress Agent Number (%) of Subjects				
	Adenosine (N=271)		Dobutamine [b] (N=13)	Combined (N=284)	
	Related To Stress Agent	Related to Tc-99m Tetrofosmin	Related to Stress Agent	Related to Stress Agent	Related to Tc-99m Tetrofosmin
Any event	39 (14)	2 (0.7)	10 (77)	49 (17)	2 (0.7)
Flushing	29 (11)	2 (0.7)	1 (8)	30 (11)	2 (0.7)
Angina pectoris	16 (6)	1 (0.4)	4 (31)	20 (7)	1 (0.4)
Dyspnea	16 (6)	0 (0)	0 (0)	16 (6)	0 (0)
Abdominal pain	8 (3)	1 (0.4)	1 (8)	9 (3)	1 (0.4)
Headache	7 (3)	0 (0)	0 (0)	7 (2)	0 (0)
Palpitation	1 (0.4)	0 (0)	6 (46)	7 (2)	0 (0)
Anxiety	3 (1)	0 (0)	0 (0)	3 (1)	0 (0)
Dizziness	3 (1)	0 (0)	0 (0)	3 (1)	0 (0)
Back pain	0 (0)	0 (0)	1 (8)	1 (0.4)	0 (0)
Crying abnormal	1 (0.4)	0 (0)	0 (0)	1 (0.4)	0 (0)
Pain	0 (0)	0 (0)	1 (8)	1 (0.4)	0 (0)
Sweating increased	1 (0.4)	0 (0)	0 (0)	1 (0.4)	0 (0)
Temperature changed sensation	1 (0.4)	0 (0)	0 (0)	1 (0.4)	0 (0)
Vision abnormal	0 (0)	1 (0.4)	0 (0)	0 (0)	1 (0.4)

[a] Subjects may have reported more than one adverse event type. All adverse events are listed by their WHO preferred term.

[b] No adverse events were considered related to Tc-99m tetrofosmin in dobutamine-treated subjects.

C) Vital Signs:

Vital signs (heart rate, systolic BP and diastolic BP) were recorded as baseline, minimal and maximal values. For each measurement, mean and standard deviation was recorded. Changes outside a specified range (>15 bpm for heart rate, >20 mm Hg for blood pressure) were also recorded and tabulated. For dobutamine stress, the greatest number of changes of BP and pulse outside the specified range occurred. Vital sign changes are summarized in Table #4 on the next page.

TABLE #4: VITAL SIGNS (From p. 893, vol. 4 of submission)

Summary of Vital Signs Data
(Combined Across Study Sites)

Vital Sign Change From Baseline	Minimum Value	Maximum Value
Heart Rate (bpm)		
N		284
Mean	—	17.0
SD		17.2
Range (min, max)		—
Systolic Blood Pressure (mmHg)		
N	282	281
Mean	-18.1	7.8
SD	18.3	16.9
Range (min, max)	—	—
Diastolic Blood Pressure (mmHg)		
N	276	273
Mean	-9.1	-1.4
SD	10.5	10.3
Range (min, max)	—	—

As expected with dobutamine and adenosine, mean increase from baseline for maximal heart rate and systolic BP were 17.0 bpm and 7.8 mmHg, respectively. The mean increase in maximal heart rate was 28.1 bpm for study site ——— , in which 11 of 41 subjects were stressed with dobutamine. Adenosine was used for all other subjects in this and the other centers. In general, review of patient data listings indicated changes in BP and heart rate to reflect the stress agents used; dobutamine and exercise were similar in producing the larger increases above the baseline values.

D) ECG's:

ST-segment deviations in 1.0 mm increments were recorded for peak stress for all study sites in Table #5 on the next page. As in Study #PR95-302, PR96,301 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 #5: STRESS ECG DATA
(reproduced from Table #13.5, p: 895, vol. 4 of submission)

Summary of ECG Results During Stress [a]
(Combined Across Study Sites)

ECG Finding	Number (%) of Subjects (N=284)
ECG Response/Other	
None	217 (76)
Arrhythmia	21 (7) [b]
Arrhythmia with 2nd degree AV block	1 (0.4)
Arrhythmia with AV block (degree missing)	2 (0.7)
AV Block	
1st degree	7 (2)
2nd degree	13 (5)
Degree missing	2 (0.7)
Degree missing/AFIB (slowing)	1 (0.4)
3rd degree [c]	1 (0.4)
Other Responses	
PACs	2 (0.7)
Sinus bradycardia (50/min at 2 min)	1 (0.4)
Sinus tachycardia	1 (0.4)
ST segment decreased 0.5-1.0 mm; Resolved within 1 minute	1 (0.4)
T wave change	2 (0.7)
PVCs	1 (0.4)
Frequent	1 (0.4)
Occasional, present at baseline	1 (0.4)
None/occasional PVCs at 3 & 4 Minutes if underwent exercise	1 (0.4)
Missing	8 (3)
ST Segment Deviation Response	
Normal (<1.0 mm)	202 (71)
1.0 - 2.0 mm	23 (8) [d]
>2.0 mm	1 (0.4)
Missing	58 (20)

[a] All abnormalities listed in the table were seen with adenosine stress unless otherwise noted.

[b] Five of the 21 subjects received dobutamine.

[c] With infusion (no AFIB/sick sinus). The subject demanded a pacemaker; not paced at rest but paced during infusion.

[d] Two of the 23 subjects received dobutamine.

Reviewer's comments: ECG data were not separated for dobutamine and adenosine stress agents.

11) SPONSOR'S CONCLUSION: (extracted from page 878 of submission)

"Intravenous administration of Tc-99m tetrofosmin under pharmacologic stress (mainly adenosine) to subjects undergoing myocardial perfusion imaging was found to be safe and well-tolerated at the doses (mean =22.67 mCi) used in this study".

12) REVIEWER'S COMMENTS

A) Trial design and protocol execution:

1) The timetable provided by the sponsor is inadequate to give the reviewer a perspective of the overall trial design and plan.
2) The protocols for individual centers are different, and do not clearly indicate if rest Myoview or Tl-201 doses are given.
3) The dosing of Myoview was not consistent from center to center.

B) Safety, toxicity and adverse events results:

1) No mention is made of recording each adverse event in the CRF, just the medical record. The CRF only asks for details for serious AE's, not nonserious ones.
2) The CRF includes only space to record systolic blood pressure, though diastolic is included in the patient data listings.
3) Only systolic BP was analyzed by pharmacologic stress agent.
4) ECG data were not separated for dobutamine and adenosine stress agents.

As Myoview is already approved for use with exercise testing in the diagnosis of coronary artery disease, the sponsor felt it unnecessary to monitor labs (hematology, chemistry and urinalysis) or pulse oximetry. Adverse events, vital signs and ECG's were recorded, and appear to reflect the stress agents used.

E) Reviewer's conclusions: With the deficiencies indicated above, this study does little to support the claim for overall safety of Myoview in the setting of pharmacologic stress.

APPENDIX 3: CLINICAL REVIEW OF STUDY sNDA #20,372
#PR96-301 (Study Report #2950) Volume 2, pp. 41-356

This document contains a review of Phase 3 Study #PR96-301: "Impact of Stress Protocol upon Myocardial Uptake and Defect Size with Tc-99m Tetrofosmin Tomographic Imaging". This study 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. This study was not intended to provide pivotal support to the indication of Myoview for scintigraphy of the myocardium in the setting of pharmacologic stress.

1) STUDY OBJECTIVE: (quoted from sponsor) This Phase 3 study was conducted "to determine the impact of stress studies (exercise or pharmacologic) on myocardial uptake and defect size as determined by Tc-99m tetrofosmin single-photon emission computerized tomographic (SPECT) imaging".

2) STUDY DESIGN: GENERAL

This study is of the open-label, single-center multiple-administration, comparative type, without placebo. Tc-99m tetrofosmin (Myoview) SPECT myocardial perfusion images obtained at rest and after pharmacologic stress with three different agents were compared. Scintigrams were interpreted by three blinded readers who reached a consensus. Safety was assessed through monitoring of adverse events, vital signs and ECG's.

3) PATIENT POPULATION

The original protocol #PR96-301 called for enrollment of 35-40 patients in one institution, from whom 25-30 were to have documented coronary artery disease (CAD) and 10 having a low likelihood of CAD. A total of 49 patients from one center actually enrolled; all were evaluable for safety and 38 for efficacy. These 38 patients included 31 with documented CAD and 7 normal volunteers (low likelihood of CAD based on negative exercise test results). The patients' age range was to be 21 years or older. Beta blockers were to be withheld for 24 hours before each stress study.

4) INCLUSION AND EXCLUSION CRITERIA

A) Inclusion criteria
   1) Adult patients 21 or more years of age.
   2) Previous negative exercise test (low likelihood of CAD) or
   3) Previously diagnosed stress-induced perfusion defects
   4) Males or non-pregnant, non-lactating females, no childbearing potential.
   5) Written and dated informed consent

B) Exclusion criteria
   1) CABG, angioplasty or MI within 6 months of study.
   2) Unstable angina within 7 days of study.
   3) Subjects with left bundle branch block or frequent PVC's (>6/min).
   4) Dilated cardiomyopathy

5) Uncontrolled hypertension (systolic.200, diastolic.120 mm/Hg).
6) Allergy or contraindication to adenosine, dipyridamole or dobutamine.
7) Congenital or valvular heart disease.

Reviewer's comment: Patients undergoing treatment for bronchospasm or taking theophylline compounds should be in the exclusion criteria.

5) STUDY DESIGN: TIMETABLE

TABLE 1: STUDY FLOW CHART (Derived from protocol)

	Pre-study	Day #1	Day #2	Day #3	Day #4	Day #5	Post-study
Prestudy history and physical	X						
Rest protocol		X*					
Exercise protocol (Bruce)			X*				
Dobutamine infusion				X**			
Dipyridamole injection					X**		
Adenosine injection						X**	
Tc-99m Tetrofosmin injection		X	X	X	X	X	
Image acquisition		X	X	X	X	X	
Image processing		X	X	X	X	X	
Vital signs and ECG	X	X	X	X	X	X	
Adverse event monitoring		X	X	X	X	X	X

* Rest and exercise Myoview imaging were performed one day apart, in either order. Adequate exercise was required for continuation in the study.

** Adenosine, dipyridamole and dobutamine stress were performed on separate days, in random order.

6) REST PROTOCOL: Imaging at rest was to be performed on a day separate from stress, 45 minutes following Myoview, 0.36 mCi/kg, given I.V. (weight limit of 114 kg). This is within the dose range specified in the labeling for Myoview.

7) STRESS PROTOCOLS: (See Figure #1 on next page)

A) Exercise protocol: The Bruce multistage protocol was to be followed, with pulse, blood pressure and a 12-lead ECG at baseline and every 2 minutes during stress, as well as continuous 3-lead ECG monitoring. Exercise was to be terminated as indicated by fatigue, progressive angina, systolic hypotension of $\geq$20 mm Hg., or sustained ventricular or supraventricular