CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-372/S-013

Medical Review(s)

a clinical review of
Myoview
(^{99m}Tc-tetrofosmin) Efficacy Supplement

NDA #20-372 SEI 013

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Medical Officer

Division of Medical Imaging and
Radiopharmaceutical Drug Products
HFD-160
U.S. Food and Drug Administration

October 4, 2002

A. Cover Sheet:

1. CLINICAL REVIEW OF NDA
   #20-372 SEI 013 Myoview Efficacy Supplement
   Submitted: 4/29/02
   PDUFA Goal Date: 3/1/03

   Nelson B. Arnstein, M.D.
   Medical Officer, HFD-160
   Review assigned: 5/9/02
   Draft completed: 8/29/02
   Review completed: 10/4/02

2. Drug names: Generic: ^{99m}Tc tetrofosmin
   Trade name: Myoview
   Chemical name: 6, 9 bis (2-ethoxyethyl)-3,12-dioxadiphosphatetradecane

3. Applicant: Amersham Health, Inc.
   101 Carnegie Center
   Princeton, N.J. 08540

4. Pharmacologic Category: Diagnostic radiopharmaceutical

5. Proposed Indication: (quoted by the applicant) "Myoview is also indicated for the assessment of ventricular function in subjects being evaluated for heart disease and/or ventricular function".

6. Dosage Forms and Route of Administration:

   5-8 mCi at rest, 15-33 mCi at stress, by intravenous bolus, for 1-day protocol
   15-33 mCi for rest and stress for 2-day protocol

7. NDA Drug Classification: 1S

8. Important Related Drugs: Tc-99m sestamibi (Cardiolite)
   Tl-201 chloride

9. Review Team:
   Project Manager: Patricia Stewart, CNMT.
   Statistics: Anthony Mucci, Ph.D.
   Clinical: Nelson B. Arnstein, M.D.
   Clinical team leader: Ramesh Raman, M.D.

10. Recommended Regulatory Action: APPROVAL

B. Table of Contents: Myoview NDA #20-372 SEI 013 Efficacy Supplement Page #

C. Executive Summary

C.1. Clinical Recommendations

C.1.a. Recommendations on Approvability

Overall Recommendation: APPROVAL (AP).

This reviewer recommends an *approval* action for Myoview for evaluation of ventricular function, based on the efficacy database, as indicated in the second section of the Executive Summary (C.2.c). Certain changes in the proposed labeling are recommended, as discussed briefly below and in detail in the Conclusions, Recommendations and Labeling section (D.8) of the review.

C.1.b. Overview of Risk/Benefit

Myoview (^{99m}Tc tetrofosmin) is a diagnostic radiopharmaceutical which has been approved for use with single-photon emission computed tomography (SPECT) imaging of the heart to evaluate myocardial perfusion. In the current efficacy supplement, the applicant is seeking to expand the indications of Myoview to include the evaluation of ventricular function (LV ejection fraction and wall motion) using ECG-gated moving cine SPECT images (GSPECT).

A discussion of risk/benefit for Myoview must focus on whether this imaging drug ultimately *helps the physician to reach a correct diagnosis*. The *risks* of using a medical imaging drug fall generally into two broad categories: 1) the risk of actually administering the drug (toxicity), and 2) the risk of the drug *providing incorrect information* (wrong diagnosis). For Myoview, the clinical safety profile is comparable to other approved SPECT myocardial perfusion agents (Tc-99m sestamibi and Thallium-201) and, when used with pharmacologic stress, reflects the use of the particular stress agents (dipyridamole or adenosine). In the context of this supplemental application, the risks of arriving at an incorrect diagnosis are those of inaccurate estimation of LV function.

The potential *benefit* of assessing LV function using Myoview is the convenience of obtaining two kinds of clinical information with one study: myocardial perfusion and LV function. The impetus for developing Myoview has been the potential to eliminate the need for a separate test to evaluate LV function in those undergoing perfusion scintigraphy.

C.1.c. Recommendations on Further Studies

No recommendations for new clinical studies are being made at this time. Based on evaluation of the submitted efficacy dataset, an additional subgroup analysis is recommended as follows:

- Subgroup analysis of efficacy in patients with ischemia during exercise stress

The reason for recommending this analysis is to test the hypothesis that underestimation of LVEF by GSPECT at low values may be due to post-stress "stunning" following exercise, reducing myocardial contraction during the stress GSPECT acquisition. In the pivotal studies, the GSPECT exam was acquired 15-45 minutes after *stress*, while the truth standard MUGA was acquired at *rest*. If residual ischemia ("stunning") and consequent LV dysfunction were present at the time of GSPECT acquisition, the GSPECT LVEF may well be reduced.

C.1.d. Recommendations for Changes in the Proposed Label

Recommendations for labeling changes include limiting the dose for the first injection of Myoview (in a 1-day imaging protocol) to 5-8 mCi as is written in the current approved label. The proposed dose limit for the first injection is 12 mCi; no explanation was provided for this increase. The new indication, *evaluation of ventricular function*, should be changed to *evaluation of left ventricular function*, as the application provided only data to support a functional assessment claim for the LV and not the RV. Other minor changes in the wording of the proposed label are also recommended.

C.2. Summary of Clinical Findings

C.2.a. Brief Overview of Clinical Program

As indicated in the previous section, Myoview is an intravenously administered diagnostic radiopharmaceutical for which the applicant is seeking an indication of assessment of ventricular function. To support this indication, the applicant has submitted results of rest and exercise (treadmill) stress Myoview gated single-photon emission computed tomography (GSPECT) imaging in 298 evaluable patients enrolled in two U.S open-label multi-center non-randomized Phase 3 trials. Assessment of left ventricular function includes global (LV ejection fraction and volumes) and regional (segmental wall motion) assessments. The trials compared Myoview GSPECT to equilibrium gated cardiac blood pool imaging (MUGA) using Tc-99m labelled red cells

The primary objective of the trials was to demonstrate that assessment of LV function could be reliably performed using Myoview GSPECT imaging. This provides important additional clinical information concerning the physiologic significance of CAD lesions as well as prognostic information in patients with non-coronary heart disease, as well as the convenience of obtaining two kinds of clinical information with one radionuclide imaging procedure.

C.2.b. Efficacy

In both studies, the applicant has demonstrated that Myoview GSPECT has acceptable sensitivity and specificity for detecting abnormalities in global LV function (as defined by an ejection fraction below 50% on the truth standard MUGA exam). The correlation of LV ejection fraction between the two modalities was also good for all blinded readers (correlation coefficients ranging from 0.70 to 0.81 in the two studies). The deficiencies in the overall efficacy database, discussed in detail in the Integrated Review of Efficacy (Section D.4), are highlighted below:

Efficacy issues of concern

- Use of accuracy as a primary endpoint

As endpoints for diagnostic efficacy, sensitivity and specificity are preferred over accuracy by the Division of Medical Imaging at FDA because they are not dependent on disease prevalence. Though sensitivity and specificity for abnormal LVEF and wall motion were considered by the applicant as secondary endpoints, they were reviewed as though they were primary for their potential supportive value.

- Comparison of a stress GSPECT study with a resting MUGA exam

In Studies MYO-301 and 303, GSPECT images acquired after treadmill exercise were compared to MUGA images obtained at rest one to five days later. Although the GSPECT acquisition was begun 15 to 45 minutes after exercise was completed, the potential still exists for residual ischemia ("stunning") to be present at the time of acquisition. This would increase the likelihood of a stress-induced wall motion or LVEF abnormality to appear on GSPECT but not the subsequent resting MUGA examination (see below).

- Underestimation of LVEF by gated SPECT in patients with poor LV function

The tendency for GSPECT to underestimate LVEF at low values seen in the pivotal trials is explained by "truncation" of the time-activity curve for GSPECT by 8-frame gating and the possibility of post-stress "stunning" reducing myocardial contraction during the stress GSPECT acquisition. This may be a direct consequence of comparing a stress GSPECT study with a resting MUGA exam (see above). However, the applicant has not adequately analyzed LVEF values in the subgroup of patients who had evidence of ischemia during stress (angina, ST-depression, myocardial perfusion defect on Myoview) to further substantiate the theory of a stress-induced wall motion abnormality as an explanation for lower stress GSPECT LVEF values. Comparing the *resting* GSPECT scans with the MUGA study would also exclude stress-induced ischemia as a contributing factor to the differences in LVEF values.

- Overestimation of LVEF in patients with small hearts

For patients with normal to high LVEF (especially women with small LV chamber sizes) the potential for GSPECT to *underestimate* end-systolic volume (and *overestimate* LVEF) exists. The dataset in this supplement has shown that most outliers whose LVEF by GSPECT exceeded the LVEF by MUGA by 20% or more were females with small hearts and MUGA ejection fractions of 72% or more. This overestimation has been reported in the literature (References #35: **Evereart et. al.** and #36: Ford et. al., vol. 29, pp. 225-244 of submission), and is most likely due to the limited resolution of the system where each voxel (volume element) represents a considerable portion of the LV volume, especially at end-systole. In the opinion of this reviewer, this provides a reasonable explanation. In any case, this problem is most likely related to limitations of the hardware and software used for imaging and not the radiopharmaceutical itself.

- Concerns raised during review of the literature

The most significant weakness of Myoview GSPECT indicated in the submitted literature was the difficulty assessing regional wall motion in hypoperfused myocardial segments. To make a reliable assessment of its motion on a cine SPECT study, one needs to visualize the myocardium. On the other hand, if a myocardial perfusion agent fails to show reduced uptake in areas of ischemia or infarction, it fails to perform as a perfusion agent. To compute LV ejection fraction and volumes, however, it is not as critical to clearly visualize all regions of the LV myocardium, and this is substantiated by the excellent overall agreement results for LVEF by GSPECT and the comparator modalities seen in the literature submitted with this application.

Efficacy conclusions

Despite the issues of concern indicated above, it is apparent that the data submitted for the two pivotal studies and the submitted literature have shown that Myoview GSPECT is a reliable tool for evaluating LV function and is adequate to support the proposed indication. As suggested by the applicant in the Integrated Summary of Efficacy, the performance of GSPECT in calculating LVEF appears to be more dependent on the software (and hardware) used for imaging than the particular perfusion agent chosen for the study.

C.2.c. Safety

The safety database includes the safety reports from the above two efficacy trials, MYO-301 and 303. Myoview was administered to 329 patients. Safety parameters evaluated include demographic data, adverse events, physical examination, vital signs and 12-lead ECG. A 4-Month Safety Update was submitted 120 days after submission of the original sNDA (8/23/02).

A total of 47 AE's were experienced by 38 of the 329 subjects receiving Myoview (11.6%). The most common AE's were chest pain (6 or 1.8%), ECG abnormalities (ST-T wave changes in 6 patients or 1.8% and nausea in 5 patients or 1.5%). Events occurring in <1% of the patients included headache, insomnia, hypertension, dizziness, fatigue and syncope. There were no deaths; 2 patients experienced serious adverse events (hypoglycemia and syncope), neither of which was considered related to Myoview by the applicant or this reviewer. One subject given Myoview withdrew due to a vaso-vagal reaction and subsequent syncope following venipuncture.

The adverse event profile for Myoview is what one may expect in a group of cardiac patients undergoing exercise stress, and is similar to that of the original Myoview NDA.

C.2.d. Dosing and labeling recommendations

The label for Myoview calls for a maximum recommended dose per injection of 33 millicuries (mCi). The recommended range is 5 to 33 mCi of radioactivity for each of 2 injections if rest and stress imaging are performed on separate days (2-day protocol). When rest and stress imaging are performed on the same day (1-day protocol), the proposed first dose is 5 to 12 mCi and the second dose is 15 to 33 mCi. As such, the upper limit of dosing for the first injection of the 1-day protocol

was increased from 8 mCi to 12 mCi. This increase was not proposed by the applicant specifically for the inclusion of GSPECT imaging; no explanation for the increase was given. Consequently, this reviewer recommends keeping the dose at 5 to 8 mCi for the first injection.

For the indications section of the proposed package insert, this reviewer also suggests changing *ventricular function* to *left ventricular function*, since the submitted data included LV evaluation only. The RV free wall, due to its reduced thickness and therefore reduced Myoview uptake, may be more difficult to evaluate using GSPECT; gated radionuclide ventriculography does not have this problem as it visualizes the cardiac blood pool and is not dependent on uptake of the tracer in the myocardium.

C.2.e. Demographics and Special Populations

Subgroup analyses of efficacy were conducted with respect to patient age, gender, cardiac medical history, LV chamber size and use of a 1-day or 2-day imaging protocol. To evaluate myocardial perfusion, images must be obtained at rest and stress; these may be obtained on the same or different days. For the 1-day protocol, a smaller initial dose of Myoview is used, followed approximately 4 hours later with the larger dose. For safety, subgroup analyses of adverse events were made on the basis of age, gender, New York Heart Association (NYHA) grade and concomitant medications. For vital signs and ECG's, subgroup analyses on the basis of age were also carried out.

Among the 336 patients enrolled in the two studies, 220 were male (65.5%) and 116 were female (34.5%), reflecting the higher incidence of CAD in males. The overall incidences of AE's for the two sexes were similar. Due to the small numbers of minority subjects (57), racial breakdowns were not provided for efficacy or safety. No specific analyses were made by height or body weight. In this supplement, Myoview was not studied in the pediatric age group (0-18 years). A pediatric indication for the drug is not being sought, and the applicant had not submitted a Pediatric Waiver Request at the time of writing this review. Studies in pregnant women were, likewise, not performed.

D. Clinical Review

D.1. Introduction and Regulatory Background

D.1.a. Clinical Background of Myoview and Myocardial Perfusion Agents

Myoview belongs to a class of radiopharmaceuticals used to image the myocardium of patients with known or suspected coronary artery disease (CAD), to assess regional perfusion and delineate areas of ischemia (reversible perfusion defects) or infarction (fixed perfusion defects). Unlike Thallium-201 chloride, a perfusion agent in use for over 30 years, Myoview and other technetium-labeled perfusion agents (for example, Tc-99m sestamibi and teboroxime) have the advantage of improved image quality and reduced radiation exposure, due to the physical properties of the technetium isotope (Tc-99m). These include a short physical half-life (6.02 hours), optimal energy photons for imaging (140 KeV) and increased photon flux as compared to thallium-201. As such, the Tc-99m perfusion agents have enjoyed widespread use over the past 10 years. The physical characteristics of Tc-99m allow for acquisition of cine (moving) tomographic (GSPECT) and planar images of the heart, gated to the electrocardiographic R-wave. Such moving images permit the reader to assess left ventricular function both quantitatively (LV ejection fraction) and qualitatively (global and regional wall motion), with the same images (and imaging agent) that were used to assess myocardial perfusion. The current efficacy supplement (#20,372 SEI-013) is seeking a new indication for Myoview: the assessment of ventricular function. The rationale for developing Myoview to obtain both myocardial perfusion and LV function information *from the same radionuclide study*, is a reasonable goal, both in terms of increased efficiency and reduced cost.

D.1.b. Proposed Indications and Basis for Development

The indications for Myoview in the proposed label are indicated below. The first two are already approved. The additional indication for Myoview sought in this Supplement is in *italics*:

INDICATIONS AND USAGE (ref. vol. 1, p. 52: Application Summary)

"Myoview is indicated for scintigraphic imaging of the myocardium following separate administrations under exercise and/or resting conditions. It is useful in the delineation of regions of reversible myocardial ischemia in the presence or absence of infarcted myocardium.

Myoview is also indicated for scintigraphic imaging of the myocardium to identify changes in perfusion induced by pharmacologic stress in subjects with known or suspected coronary artery disease.

Myoview is also indicated for the assessment of ventricular function in subjects being evaluated for heart disease and/or ventricular function."

To evaluate myocardial perfusion, images are acquired following injection of Myoview on two occasions: at rest and at peak stress (exercise or pharmacologic). The dose is measured in millicuries (mCi) or megabecquerels (MBq) of injected radioactivity. In the current approved label, 5 to 8 mCi (185-296 MBq) of Myoview is administered for the first of 2 injections (at rest or following stress). Four hours later, a second dose of 15 to 33 mCi (555 to 1221 MBq) is given (one-day protocol). In some patients who are large or obese, imaging on two separate days is performed, with 5 to 33 mCi (185 to 1221 MBq) given for each injection. Proposed changes in the label include increasing the range of the first dose of Myoview to *5-12 mCi* for the one-day protocol. To support the new indication, the applicant has conducted 2 prospective, active-controlled trials (MYO-301 and 303).

D.1.c. Regulatory History, Meetings and Milestones in Development of the LV Function Indication

The following summary of the regulatory history and milestones for this agent are taken in part from Vol. 27 (Integrated Summary of Efficacy, pp. 12-13), as well as minutes and notes for meetings and teleconferences with the applicant over the course of development (from the HFD-160 Division File). Issues of concern which had arisen during the course of designing the pivotal studies were communicated to the applicant at various meetings prior to submission of this efficacy supplement.

This section pertains only to the development of Myoview as an agent *for assessment of ventricular function*; the myocardial perfusion indication (using exercise stress) is discussed in the Division reviews of the original NDA, approved February 1996. The addition of pharmacologic stress to the labeling was approved November of 2001; this indication is discussed in Division reviews of Efficacy Supplement #20,372 SEI-003.

Clinical Study Dates

- **March 20, 2001.** Study MYO-301 enrolment begun
- **March 30, 2001.** Study MYO-303 enrolment begun
- **January 27, 2002.** MYO-303 study completed
- **March 1, 2002.** MYO-303 study report completed
- **March 3, 2002.** MYO-301 study completed
- **March 29, 2002.** MYO 301 study report completed

Protocol and Amendment Submissions (under IND #[redacted])

- **March 5, 1999.** Submission of *draft* protocol entitled "An Open-label, Multicentre Phase 3 Trial Evaluating Ventricular Function as Assessed by Left Ventricular Ejection Fraction and Wall Motion Using Technetium-99m Tetrofosmin Injection Gated SPECT Imaging" (Serial #043).
- **November 15, 2000.** Submission of protocol MYO-301 and MYO-303 (Serial #055).
- **March 2, 2001.** Amendment A-01 submitted (Serial #065). Several safety endpoints requested by FDA were addressed, and timepoints of assessments clarified.. MUGA scheduling was changed from [redacted] hours to 1-5 days after the last Myoview dose at request of FDA.
- **June 27, 2001.** Submission of response to FDA Comments of May 3, 2001 (Serial #076).* The applicant acknowledged the potential loss of sensitivity of gated SPECT for detecting stress-induced LV dysfunction caused by the 15-45 min. acquisition delay after dosing with Myoview. The applicant also explained that first pass Myoview LVEF and wall motion studies would not be practical due to the need for high-sensitivity [redacted] gamma cameras.
- **August 15, 2001.** Amendment A-02, submitted (Serial 080).* For primary endpoints, this amendment replaced sensitivity and specificity with accuracy of GSPECT for LVEF measurements. The proposed sample size remained unchanged at 102. The number of blinded readers for the MUGA exam was increased to three for the purpose of reaching a consensus.
- **September 19, 2001.** Amendment A-03, submitted (Serial 082).* This added the inclusion criterion of ejection fraction of <40% by echo within 1 week of Myoview dosing. This was in response to an FDA request to diversify the patient population. In this amendment, the planned sample size was also increased to 170.

* Amendment submitted after study enrolment began

Teleconferences and Meetings between Amersham Health and the Division

- **March 12, 1999.** Teleconference to discuss draft nature of the protocol submitted for FDA comments.
- **April 20, 1999.** Teleconference to further discuss draft protocol.
- **May 4, 2000.** Teleconference to discuss agent of choice for gold standard; agreement was reached that [redacted] was not appropriate as it has not been approved for LV function. Tc-99m RBC suggested as an alternative, and was agreed to during this meeting.

- **April 23, 2001.** Teleconference to clarify two revisions to Protocol MYO-301/303 proposed in Serial #065 and #068.
- **April 24, 2001.** Teleconference to clarify additional revisions to protocol MYO-301/303 submitted March 2, 2001 (Amendment A-01, serial #065).

Clinical Comment Facsimiles Sent to the Applicant

- **April 15, 1999.** Clinical comments regarding draft protocol sent to applicant.
- **April 25, 2001.** Draft clinical comments regarding applicant's responses faxed to Division January 12, 2001.
- **May 3, 2001.** Clinical comments, responded to in Serial #076. Concern was raised that the sensitivity of gated SPECT for detecting stress-induced LV dysfunction may be reduced because of the 15-45 minute delay of acquisition after dosing with Myoview. Also, the applicant was asked why first pass Myoview LVEF and wall motion studies were replaced by equilibrium ECG-gated SPECT imaging.

sNDA Submission

- **Apr. 13, 2002**: Submission of the Myoview efficacy supplement (NDA #20-372 SEI 013).

D.2. Description of Clinical Data Sources

D.2.a. Sources of Data for Review and Tables of Clinical Trials

The database for sNDA #20-372 SEI-013 includes the applicant's Clinical Trial Reports (CTR's) for 2 studies completed at the time of submission. The studies also constitute the safety database; data therefrom are pooled in the Integrated Summary of Safety for each of the safety parameters analyzed. A 4-Month Safety Update was submitted 120 days after the time of sNDA submission. Those trials completed at the time of submission are listed in Table #2.a.1 below. Table #2.a.2 gives the salient design features of the 2 pivotal trials in the database: MYO-301 and MYO-303.

TABLE #2.a.1: Completed Studies

Category	Studies	Number of Subjects Exposed	
		Myoview	RBC
Pivotal clinical studies	MYO-301	142	136
	MYO-303	187	175
Total Patients		329	311
Total Healthy Volunteers		0	0
Total Subjects		329	311

TABLE #2.a.2: Trials in the NDA Database: Salient Features

FEATURE	MYO-301	MYO-303
Study design	Phase 3 U.S.A. open-label multi-center parallel-comparative	Phase 3 U.S.A. open-label multi-center parallel-comparative
Study objectives	To evaluate Myoview gated SPECT as compared to MUGA for evaluating LVEF and regional wall motion	To evaluate Myoview gated SPECT as compared to MUGA for evaluating LVEF and regional wall motion
No. of subjects	145 subjects enrolled 142 exposed to Myoview, evaluable for safety 127 evaluable for LVEF 124 evaluable for wall motion	191 subjects enrolled 187 exposed to Myoview, evaluable for safety 171 evaluable for LVEF 171 evaluable for wall motion
No. of centers	10	9
Entry criteria	Subjects ≥ 18 years old with known or suspected heart disease and/or LV dysfunction	Subjects ≥ 18 years old with known or suspected heart disease and/or LV dysfunction
Rest dose	15-24 mCi (2-day) or 5-8 mCi (1-day)	15-24 mCi (2-day) or 5-8 mCi (1-day)
Stress dose	15-24 mCi	15-24 mCi
Blinded read	Yes (3 independent readers)	Yes (3 independent readers)
Truth standard	Radionuclide ventriculography with Tc-99m labeled RBC — 15-20 mCi	Radionuclide ventriculography with Tc-99m labeled RBC — 15-20 mCi
Efficacy endpoints (primary)	LVEF in all subjects (accuracy) LV global wall motion	LVEF in all subjects (accuracy) LV global wall motion
Efficacy endpoints (secondary)	LVEF in pts. with LVEF < 50% (sensitivity) LVEF in pts. with LVEF ≥ 50% (specificity) LV segmental wall motion	LVEF in pts. with LVEF < 50% (sensitivity) LVEF in pts. with LVEF ≥ 50% (specificity) LV segmental wall motion
Safety evaluation	History, physical exam, AE's ,vital signs, ECG (12-lead), urine pregnancy test	History, physical exam, AE's ,vital signs, ECG (12-lead), urine pregnancy test
Sensitivity: LVEF (pooled readers)	87.5%	81.0%
Specificity: LVEF (pooled readers)	77.3%	84.4%
Accuracy: LVEF (pooled readers)	81.9%	83.0%
Sensitivity: wall motion (pooled readers)	86.2%	84.8%
Specificity: wall motion (pooled readers)	74.7%	80.2%
Accuracy: wall motion (pooled readers)	80.4%	81.9%

(Ref. derived from Medical Officer's Fileability Summary, p. 2)

D.2.b. Subject Enumeration and Demographics

As indicated above, of the 336 patients enrolled, 329 were exposed to Myoview, 311 of whom were also exposed to Tc-99m labelled RBC in 2 clinical trials completed at the time of submission. The demographic breakdown of these is given in the Overview of Safety (Section D.5).

D.2.c. Post-marketing Experience

Myoview was approved for myocardial perfusion imaging with exercise stress in Europe in 1993 and the United States in 1996. The tracer was approved for use with pharmacologic stress in December of 2001. Since approval of the original NDA in Europe, approximately 4,049,000 subjects have been dosed with the drug, and 228 spontaneous adverse drug reactions (143 spontaneous case reports) have been reported. Among these adverse reactions, approximately 76% have occurred in subjects undergoing exercise stress while 24% happened in subjects undergoing pharmacologic stress. Since original NDA approval, no new risks have been identified, and no labeling changes have been made on the basis of spontaneous adverse event reports. See Section F.2: Review of 4-Month Safety Update for further details. The most common reactions are listed in Table #2.c.1 below:

TABLE =2.c.1: Most Common Adverse Drug Reactions since Marketing by Body System: N, (%)

ADVERSE EVENT WHO Body System	**# of Events**
Total	228
Body as a Whole	
Allergic reaction	25
Pain	6
Fever	5
Anaphylactoid reaction	4
Skin and appendages	
Rash	22
Urticaria	5
Pruritus	4
CNS, Peripheral Nerves	
Dizziness	2
Headache	2

(Ref. derived from p. 88, vol. 1)

D.2.d. Use of Myoview GSPECT in the Medical Literature

References from the literature submitted with the application include 22 publications. Although these were not specifically intended to support the efficacy claim, these literature references were consulted for review, and are discussed in Section D.4.d (efficacy) and D.5.e (safety).

D.3. Clinical Review Methods and Financial Disclosure

D.3.a. Overall Approach to the Review

The two pivotal trials are discussed in Section D.4.c (Detailed Review of Pivotal Clinical Trials). Literature articles reviewed for potential efficacy support are discussed in Section D.4.d. The safety database is reviewed as a single unit in the Integrated Review of Safety (Section D.5).

1. Approach to the Efficacy Review

For the indication of evaluating LV function, the applicant has conducted 2 identical pivotal studies: MYO-301 and MYO-303. In Section D.4.c, the common protocol is described, followed by separate presentations of the efficacy results. The two trials are then discussed together at the end of the subsection, with a reviewer's assessment and conclusions. In addition, 22 articles were submitted as references in Volume 26 of the submission. Though not indicated by the applicant as being an integral component of the efficacy database for the ventricular function indication, selected articles were reviewed for their potential supportive value. The overall conclusions, issues of concern and reviewer's recommendations are discussed together in the final subsections of the Integrated Review of Efficacy (D.4.e and f) along with input from the statistical reviewer.

2. Approach to the Safety Review

As indicated above the safety review (Section D.5) is focused on the applicant's Integrated Summary of Safety (ISS) as a starting point, with further review of data from individual studies as needed. In addition, the 22 submitted articles from the literature were reviewed for safety information. A 4-Month Safety Update was submitted 120 days after original submission of the sNDA. There were no studies of safety in special populations.

D.3.b. Documents Consulted in Review, Electronic Submission

The documents reviewed include the sNDA submission itself and clinical/statistical Correspondences from the applicant received since submission of the NDA in April of 2002. In addition, clinical reviews of protocols submitted under IND [redacted] minutes of meetings with the applicant (Phase 3 trial design and pre-NDA) in the Division File, and faxes sent to and from the applicant were consulted as needed. To assist in review, the *Guidance for Industry: Developing Medical Imaging Drugs and Biologics* was consulted, as well as labeling for approved myocardial perfusion SPECT agents. This review is written according to guidelines presented in the Clinical Review Template (Interim Directive) of March 30, 2001.

The sNDA submission consists of 72 volumes. Sections of the application formatted according to 21 CFR 314.50 are as follows (Table 3.b.1 below):

TABLE #3.b.1: Sections of the Application and Numbering of Volumes

Section #	Item	Location: volume (s), page(s)
1	Index to the Application	Volume #1, Index
2	Labeling	Volume #1, pp. 27-38
3	Application Summary	Volume #1, pp. 39-89
4	Chemistry, Manufacturing and Controls Section	Not applicable
5	Nonclinical Pharmacology/Toxicology Section	Not applicable
6	Human Pharmacokinetics and Bioavailability Section	Not applicable
7	Microbiology Section	Not applicable
8	Clinical Data Section	Volumes # 2 - 35
9	4-Month Safety Update	Submitted 8/23/02
10	Statistical Section	Volumes # 36 - 68
11	Case Report Tabulations	Volumes # 69 - 71
12	Case Report Forms: Deaths, Serious AE's, Withdrawals	Volume # 72
13-20	Administrative Sections	Volume #1, pp. 1-20
	Form 356h	Cover Letter

All sections of the application were available to this reviewer. Electronic materials submitted included CD-ROMS containing the SAS statistical datasets, which were available for review.

D.3.c. Selection of DSI Audit Sites for Inspection

The following four sites were selected for DSI audit. Three are clinical sites; the fourth is the core lab where blinded reads for efficacy were conducted (See DSI report by T. Ju, M.D. for details). At the time of review (30 August. 2002), results of these audits were not available.

TABLE #3.c.1: Sites Selected for DSI Audit

Protocol #	Principal Investigator	Site
MYO-303	Steven L. Edell, D.O., FACR	Delaware SPECT Imaging Center, Newark, DE (#040)
MYO-303	Frederick Weiland, M.D.	Sutter-Roseville Medical Center, Roseville, CA (#049)
MYO-301	Phillip Koren, M.D.	Cardiovascular Assoc. of the Delaware Valley, Haddon Hts, NJ (#013)
Both	Core laboratory	[redacted]

D.3.d. Informed Consent and Ethical Standards

Informed consent forms were included with the protocol for each study (vol. 5, pp. 160-166 for MYO-301 and vol. 16, pp. 152-159 for MYO-303). The consent forms themselves were similar, but not identical. In the protocols, it was stated that written consent was to be obtained according to the requirements of 21 CFR 50.20-50.27 and the forms inspected by the IRB's of the respective institutions. Each investigator was to maintain a copy of the consent form on file. Both studies in this sNDA appear to this reviewer to comply with accepted ethical standards.

D.3.e. Financial Disclosure of Investigators

A Form FDA 3454 (Financial Disclosure Information) was submitted by the applicant in compliance with 21 CFR 54. (Vol. 1, p. 21) On the form, the Vice President of Global Clinical Research has stated that the clinical investigators and blinded readers (list supplied with the form) have not entered any financial arrangement where compensation to the investigator could be affected by the outcome of the clinical studies. In the List of Investigators, information for each investigator includes name, study and study center number only. A complete list of investigators was submitted with each clinical study report. No disclosures of financial conflicts-of-interest were reported. Based on the information provided, this reviewer has not seen any information which would cast doubt on this absence of disclosures.

D. 4. Integrated Review of Efficacy

D.4.a. Introduction, Applicant's Claim and Brief Overview

As indicated in Section C of this review (Executive Summary), Myoview is an intravenously-administered radiopharmaceutical approved for imaging myocardial perfusion, identifying areas of ischemia and infarction. In the current submission, the applicant proposes to expand the indications of Myoview to include the evaluation of ventricular function. In the proposed labeling, the addition of the function claim reads as follows (quoted from the applicant):

- Proposed Indication: "Myoview is also indicated for the assessment of ventricular function in subjects being evaluated for heart disease and/or ventricular function".

In NDA #20,372 SEI 013, the applicant has submitted in support of efficacy the results of two single-center crossover active-comparator studies, MYO-301 and 303. The overall approach to the efficacy review is discussed in Section D.4.b. The two pivotal studies are reviewed in detail in Section D.4.c. In Section D.4.d, is a discussion of literature articles included with the application. Although these articles were not specifically submitted to support efficacy claims for Myoview, they were reviewed for their potential supportive value according to criteria established in the *Guidance for Industry: Providing Clinical Evidence for Effectiveness for Human Drug and Biological Products*. The overall conclusions and reviewer's recommendations are then discussed together in subsection D.4.e along with input from the statistical reviewer in subsection D.4.f.

Briefly, the two pivotal studies were designed to assess the ability of gated SPECT imaging (GSPECT) using Myoview to evaluate LV function, both globally (LV ejection fraction) and regionally (segmental wall motion). By comparing the quantitative values for LVEF and segmental wall motion scores with those obtained by equilibrium gated cardiac blood pool imaging (MUGA) using tagged red cells, agreement can be assessed, and sensitivity/specificity for detecting abnormalities in LVEF (<50%) or wall motion (hypokinesis, akinesis, dyskinesis) can be evaluated. Along with selected articles from the literature, the two pivotal studies MYO-301 and 303 have provided, in the opinion of this reviewer, data sufficient to recommend approval of this supplementary Myoview application for the indication of evaluating left ventricular function.

D.4.b. Approach to the Efficacy Review

As indicated in Section D.4.a, the applicant has conducted 2 studies to support efficacy claims of Myoview to evaluate ventricular function. The two pivotal studies are reviewed in detail in the next subsection of the review (#D.4.c). The salient characteristics of the trials are listed in Table #4.b.1 below and in more detail in Table #2.a.2 in Section D.2 (Description of Clinical Data Sources). The design of the studies was identical.

TABLE #4.b.1. Evaluation Of Efficacy: Phase 3 Pivotal Studies

Study	N (enrolled)	Location	Study design	Myoview doses (mCi)	Comparator	
					Agent	Dose (mCi)
MYO-301	145 patients	USA 10 centers	Single-blind, parallel comparative, crossover	15-24 mCi stress 5-8 mCi rest (1-day) 15-24 mCi rest (2-day)	Tc-99m labelled RBC —	15-20 mCi
MYO-303	191 patients	USA 9 centers	Single-blind, parallel comparative, crossover	15-24 mCi stress 5-8 mCi rest (1-day) 15-24 mCi rest (2-day)	Tc-99m labelled RBC —	15-20 mCi
All study agent doses administered as an IV bolus injection						

(derived from Table E, page 179, vol. 1 of the submission)

The evaluation of efficacy in the pivotal studies was made on the basis of the primary variables. *LV ejection fraction* and *LV wall motion* as compared to a truth standard (equilibrium radionuclide ventriculography, using Tc-99m radiolabeled red cells and called MUGA for *mu*ltiple gated *a*cquisition). In both studies, MUGA alone was used as the truth standard. The focus of this review is therefore on the ability of Myoview GSPECT to estimate LV ejection fraction and evaluate wall motion, as compared to MUGA.

As *primary endpoints*, the applicant has chosen the *accuracy* of GSPECT as compared to MUGA in evaluating LV ejection fraction (normal ≥50% vs. abnormal <50%) and subject-based wall motion (presence/absence of a wall motion abnormality). *Secondary* efficacy endpoints included separate determinations of *sensitivity* and *specificity* for normal/abnormal GSPECT LVEF as compared to MUGA, and *accuracy* of regional wall motion assessments for each of 5 regions of the LV (anterior, lateral, inferior, septal and apical).

In addition to the 2 pivotal Phase 3 studies, the applicant has submitted in Volume 26 of the application 22 articles from the medical literature. Of the articles submitted, all were identified as investigating Myoview imaging of the human heart. Many of the submitted articles compared GSPECT with another imaging modality (MUGA, gated MRI, echocardiography or contrast left ventriculography). After stepwise elimination of articles using criteria listed in the *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biologic Products*, five of the articles remained to be considered for their potential to provide additional support for the efficacy claim. In Section D.4.d, these 5 articles are reviewed, along with a discussion of the FDA *Guidance* criteria used to select and evaluate them.

D.4.c. Efficacy Review of Pivotal Clinical Trials

Study Title: "An Open-label, Multicentre Phase 3 Trial Evaluating Ventricular Function as Assessed by Left Ventricular Ejection Fraction and Wall Motion Using Technetium-99m Tetrofosmin Injection Gated SPECT Imaging" (MYO-301, MYO-303)
(The same title is used for both protocols, which are identical.)

1. Study objectives and trial design (both studies)

Studies MYO-301 and 303 were two pivotal Phase 3 trials to support the indication of evaluating LV function sought for ^{99m}Tc-tetrofosmin (Myoview). The studies were multi-center (U.S.A.), open-label, 3-administration (2 Myoview, 1 ——— Tc-99m labelled RBC), crossover trials with interpretation of gated SPECT (GSPECT) scans by 3 off-site independent blinded readers as well as the principal investigator. The primary objective was to evaluate the efficacy of Myoview in assessing ventricular function (LV ejection fraction and wall motion) using GSPECT. Radionuclide ventriculography (MUGA) using Tc-99m tagged red cells served as a truth standard. For the purpose of this review, the protocol is described in some detail, followed by a presentation of the clinically relevant results from each trial. A discussion of the study design and efficacy results follows. Safety testing is discussed in the Integrated Review of Safety (Section D.5).

1:1. Entry criteria: Male or female patients ≥ 18 years of age with known or suspected heart disease and/or ventricular dysfunction. To assure study of a broad range of LV dysfunction, a new inclusion criterion, the requirement for LVEF ≤40% by *echocardiogram* within 1 week of entry was added after the study began (See Section D.1.c). Unstable or life-threatening medical conditions, inability to exercise, atrial fibrillation, hypersensitivity to Tc-99m agents, unstable angina or heart failure, coronary bypass within 6 weeks or angioplasty/stent within 1 week of entry, or other severe medical or psychiatric conditions were among the exclusion criteria.

1:2. Dosing and exercise stress:

Tc-99m tetrofosmin was given either for a 1-day rest/stress SPECT (276 patients) or a 2-day rest/stress SPECT procedure (53 patients). The 2-day procedure was used at the discretion of the investigator in patients with obesity or with large breasts or pectoral muscles. Each injection of Tc-99m tetrofosmin was to be given in 0.3 to 0.5 ml sterile water as a bolus via an IV line. Injection of the study drug is to be followed by a 2 to 10 ml saline flush. Exercise was on a treadmill, following the Bruce, Naughton or other protocol (indicated in CRF), and vital signs/12-lead ECG's taken every 2 minutes.

a) For the 1-day procedure, 9-12 mCi of Myoview was to be given, followed 30-60 minutes later by resting gated SPECT imaging. One to 4 hours after the rest dose, the patient underwent treadmill exercise and a 15-25 mCi stress dose of Myoview was given at peak stress or at the discretion of the supervising physician.
b) For the 2-day procedures, either rest or stress Myoview studies using 15-25 mCi for each were performed (stress-rest or rest-stress). In selected cases, the rest dose was 9-12 mCi. The choice was made according to clinical protocol at each study center. Exercise was according to the same protocol as in (a) above, with Myoview given at peak stress or at the discretion of the supervising physician.

1:3. Imaging procedure:

Gated rest cardiac SPECT was to be acquired beginning at 30-60 minutes after Myoview dosing and stress SPECT at 15-45 minutes after injection. Only the post-*stress* GSPECT exam was used for the efficacy analysis. A first-pass acquisition was not taken. A ——— gamma camera fitted with a low energy, high resolution parallel hole collimator, peaked at 140 KeV and 20% window was used. For the ——— camera, 60 projections and for the 2 headed

system, 90 projections were acquired over a 360-degree arc. For single-headed units 64 projections over 180 degrees (LPO to RAO) was acquired. All images were stored in a 64 x 64 matrix format. The volume data were reformatted on-site into short, vertical long and horizontal long axis planes as well as polar maps for the readers. The original imaging data for each MUGA and GSPECT study were then transferred to a Core Laboratory, where further processing was done using FDA-approved software to calculate the LVEF from the volume data for the GSPECT and from the LAO view for the MUGA scan.

1:4. Blinding: All GSPECT images at the core lab were interpreted by 3 independent blinded readers unaware of patient history and diagnosis (off-site) and the principal investigator (on-site).

1:5. Radionuclide ventriculography (MUGA):

After injection of 15-20 mCi of · ——_ · labelled red cells prepared by the *in-vitro* method, imaging was performed using a gamma camera peaked at 140 KeV (20% window) and gated to the ECG R-wave. An R-R interval window of 10-40% for arrhythmia filtration was used. Three views (anterior, best-septal LAO, LPO 30^0) were acquired, for 16-32 frames of at least 200K each. The ROI for LV activity is generated semi-automatically by the computer. The MUGA scan was performed *at rest* 1 to 5 days after the second Myoview dose.

1:6. Efficacy endpoints:

The *primary efficacy endpoints* for both studies were 1) LVEF as determined by GSPECT and computed at the core lab for *all* of the *stress* Myoview images, and 2) *subject-level* wall motion assessment of the stress GSPECT images by the blinded readers. The cutoff of 50% for normal/abnormal LVEF values was then used to determine the *accuracy* (% agreement) of GSPECT assessments (normal or abnormal) with respect to the MUGA assessments.

The *secondary efficacy endpoints* included 1) separate LVEF determinations by GSPECT for the stress Myoview images in those subjects with LVEF <50% by MUGA (*sensitivity*), 2) LVEF determinations by GSPECT in those with LVEF ≥50% by MUGA (*specificity*); and 3) *region-level* wall motion assessment of the stress GSPECT images by the blinded readers. (See section 4: Reviewer's Discussion, Issues of Concern and Conclusions, p. 30).

1:7. Image analysis and interpretation:

a) Gated SPECT image interpretation and correlation: Three independent observers trained in Nuclear Cardiology read the images at a core laboratory, recording LVEF and regional wall motion (RWM). Readers were blinded as to patient identification, clinical history, gender and the study protocol. Images presented to the readers included a cine rotating planar image display and reconstructed slices in short and vertical/ horizontal long axes. Slices were displayed in a linear gray-scale, with the option to switch to color. Gated slices for wall motion assessment and ROI's for ejection fraction measurement were also presented to the reader. For LVEF, values were computed with and without background subtraction. The cardiac cycle was divided into 8 frames, from which the frames most closely representing end-systole and end-diastole were selected. The volumes from these images were then used to compute LVEF. Image quality was recorded as "optimal", "suboptimal but diagnostic" and "non-diagnostic". The cardiac images were divided into the following segments: lateral, anterior, septal, inferior, apical. For RWM, each segment was qualitatively graded 1 for normal, 2 for hypokinesis, 3 for akinesis and 4 for dyskinesis. Reasons for a technically inadequate study included patient motion, insufficient count rate, diaphragmatic or breast attenuation and technical artifacts. If either the SPECT or MUGA images were considered "non-diagnostic", the subject was eliminated from the efficacy analysis, but the reason for the suboptimal image was recorded in the CRF and included in the subject data listings. If the reader did not agree with ROI's generated by the technologist at the Core Lab, he/she was asked to redraw it and recalculate the LVEF.

b) MUGA image interpretation and correlation: Three blinded readers (different from those reading GSPECT) trained in Nuclear Cardiology read the images at a core laboratory, recording LVEF and regional wall motion (RWM). Readers were blinded as to patient identification, clinical history, gender and the study protocol, but reached a consensus (unlike the Myoview SPECT blinded read). Images presented to the readers included cines of all 3 views, computer-generated ROI's and LVEF calculations. Readers assigned a wall motion score from 1 to 4 (normal to dyskinetic) for each of the 5 segments listed in #7 above. If the reader did not agree with the ROI, he/she redrew it and recalculated the LVEF. For the MUGA, LVEF was calculated based on dividing the RR interval into 16 to 24 frames, and choosing the end-systolic and end-diastolic LAO from these images.

1:8. Efficacy parameters and statistical methods: (See Statistical Review by A. Mucci, Ph.D.)

Agreement of LV ejection fraction (accuracy) between SPECT and MUGA was analyzed as a *primary endpoint*, with scatterplots and Bland-Altman plots (x = mean of paired LVEF observations; y = difference between LVEF observations). A normal LVEF, as indicated above, is $\geq$50%. Receiver-operating characteristic (ROC) analysis was used to determine the *secondary endpoints* of sensitivity and specificity of gated SPECT at various threshold values relative to the normal or abnormal LVEF as determined by MUGA. The inherent differences between gated SPECT and MUGA were expected to produce a systematic bias z_o so that the threshold value for a normal GSPECT was LVEF = 50% + z_o. Goal #1 was to determine the proportion of abnormal MUGA (LVEF <50%) subjects who were correctly assessed as abnormal by Myoview GSPECT (LVEF < 50% + z_o). Goal #2 was to determine the proportion of normal MUGA subjects who were correctly assessed as normal by GSPECT (LVEF $\geq$ 50% + z_o).

As a *primary endpoint*, regional wall motion (RWM) was evaluated on a *subject level*. As described in #1:7 above, each of five myocardial wall areas was graded as 4=dyskinetic; 3=akinetic, 2=hypokinetic and 1=normal. For the purpose of a binary analysis, 2, 3 and 4 were collapsed into an "abnormal" category. The proportion of patients *p* whose normal/abnormal subject-level RWM assessments were concordant were computed for the two procedures. Calculation of *p* was done for each of the 3 blinded readers. Independent readers were grouped in pairs to compute the strength of agreement in detecting subject-level RWM abnormalities using the kappa statistic (κ).

As a *secondary endpoint*, RWM was assessed on a *segment level*. Five wall motion scores were generated for each patient, for on-site MUGA and GSPECT reads, the consensus MUGA read and each of the independent blinded SPECT reads. The agreement in RWM assessments between the two procedures was the proportion *p* of patients whose normal/abnormal regional assessments were in concordance, for each of the 5 regions of the myocardium.

1:9. Safety evaluation

The safety evaluation of patients in Studies #MYO-301 and 303 included adverse event reporting through general questioning, physical exam, vital signs (temperature, pulse, BP and respirations) captured at 10 minutes before and 10 minutes after each dose, and 10 minutes before MUGA tagged red cell injection. ECG's (12-lead) were captured at the same times as vital signs, and 24 hours post-stress dose. Laboratory evaluations were not taken as Tc-99m tetrofosmin has already been approved in this group of patients.

A full discussion of the safety results of this and the other studies in the NDA #20,372 SEI-013 safety database can be found in Section #D-5: Integrated Review of Safety.

2. Results: Study MYO-301:

2:1. Demographics and Baseline Characteristics

A total of 145 patients at 10 U.S. centers enrolled in MYO-301. Three patients were withdrawn prior to the first Myoview dosing, leaving a safety population of 142. One patient was withdrawn due to the use of pharmacologic stress; 1 did not have a gated SPECT, leaving 140 to have an evaluable GSPECT. MUGA was acquired in 136, of which 1 was suboptimal due to poor RBC tagging. The remaining 135 comprise the efficacy population.

Among the 145 patients, 135 (93.1%) had a cardiovascular history; heart failure was present in 65 (44.8%); angina pectoris in 71 (49.0%); prior MI in 57 (39.3%); prior CABG in 42 (29.0%) and prior PTCA in 54 (37.2%).

Demographics for the enrolled population are summarized in Table #4.c.1 below:

TABLE #4.c.1: Demographic Information: Study MYO-301

Demographic Parameter		Patients (145)
Sex:	Male	102 (70.3%)
	Female	43 (29.7%)
Age (years):	Mean ± SD	61.2 ± 11.7
	Range	30 – 88 years
	<65	82 (56.6%)
	65 – 80	56 (38.6%)
	>80	7 (4.8%)
Race:	White	117 (80.7%)
	Black	21 (14.5%)
	Other	7 (4.8%)
Weight (lb.)	Mean	85.0 ± 19.4
	Range	52.2 – 149.7 kg
Height (in.)	Mean	170.7 ± 9.9
	Range	137.2 – 190.5 cm

(Ref. vol. 2, p. 210)

2:2. Dosage and Administration

In Study MYO-301, 140 patients received both doses of Myoview, and 135 also underwent a satisfactory MUGA examination, and comprise the efficacy population (see above). Two patients received only 1 dose of Myoview (stress). For the resting images, a large majority (139) received the low Myoview dose (mean 9.4 mCi, range —— mCi). Three patients received the high rest Myoview dose (mean of 26.7 mCi, range —— mCi). For stress images in 142 patients, the mean dose was 23.3 mCi, range —— mCi. For the MUGA study, the range of —— doses among the 136 patients was specified as 15-20 mCi, however, the individual doses were not reported in the summary tables or patient data listings.

2:3. Efficacy Results: Study MYO-301

1. Datasets analyzed: From the 140 patients who underwent rest and stress Myoview GSPECT and 135 undergoing MUGA, several patients were eliminated from the efficacy analysis due to suboptimal MUGA or GSPECT exams as read by the blinded readers (3 readers for the GSPECT images and 3 for the MUGA scans). Table #4.c.2 below indicates the denominator of remaining evaluable patients for each reader of the GSPECT images:

TABLE #4.c.2: Evaluable Patients: Study MYO-301

ENDPOINT	Reader 1	Reader 2	Reader 3
LVEF	127	121	127
Wall Motion	124	119	124

(Ref. derived from Figure 3, vol. 2, p. 215)

2. Efficacy analyses: sensitivity, specificity

The results of comparing the Tc-99m tetrofosmin gated images against the truth standard (MUGA) were reported for LV ejection fraction (Endpoint 1) and global LV wall motion (Endpoint 2). LVEF values were scored as normal (>50%) or abnormal (<50%); wall motion was scored abnormal if hypokinesis, akinesis or dyskinesis were seen anywhere in the LV.

a. LVEF: The table below indicates the normal and abnormal readings for both SPECT by individual readers and MUGA by consensus, presented as 2x2 tables (highlighted in gray) to compute sensitivity and specificity. The results appear comparable among the readers, but show a trend for GSPECT to underestimate LVEF as compared to MUGA.

TABLE #4.c.3: 2x2 Tables of LVEF (Normal or Abnormal) for MUGA (Consensus) and GSPECT (3 blinded readers)

	Reader 1 GSPECT Assessment			**Reader 2 GSPECT Assessment**			**Reader 3 GSPECT Assessment**		
Consensus MUGA Assess.	Normal n	Abnormal n	Total n	Normal n	Abnormal n	Total	Normal n	Abnormal n	Total n
Normal	53	17	70	53	14	67	54	16	70
Abnormal	7	50	57	7	47	54	7	50	57
Total	60	67	127	60	61	121	61	66	127
Sensitivity	87.7%			87.0%			87.7%		
Specificity	75.7%			79.1%			77.1%		

(Ref. derived from Table 11.3.1.1, p. 219, vol. 2)

Reporting of numerical LVEF values was in the form of scatter plots of consensus MUGA LVEF vs. GSPECT LVEF for each reader. In addition, Bland-Altman plots were generated; these show the *average* LVEF (consensus MUGA + GSPECT for each reader / 2 [%]) on the x-axis, and the *difference* (consensus MUGA – GSPECT [%]) for each reader on the y-axis. The Bland-Altman plot is designed to determine the limits and level of agreement between the two modalities, to uncover trends of LVEF for one modality being higher than the other, and any relationship of this trend to the LVEF values themselves. For the 3 readers, both scatter and Bland-Altman plots were very similar, though there was a tendency for GSPECT to *underestimate* LVEF at low values. The use of 8 frames rather than 16 for ECG gating of SPECT images offers a good explanation, as such gating tends to "truncate" the end-systolic volume part of the time-volume curve. Software limitations may also offer a partial explanation. Since the GSPECT was done 15-45 minutes after *exercise* and MUGA was done at *rest,* LVEF values may differ (GSPECT *lower* at stress in CAD patients due to ischemia and resulting LV dysfunction).

Patients whose LVEF values were abnormal on one modality and normal on the other, and whose quantitative values differed by 10% or more were considered "outliers". For Reader 1, there were 19 out of 124 patients (15.3%); for Reader 2, 16 out of 119 patients (13.4%) and for Reader 3, 17 out of 124 patients (13.7%). The scatterplots showed most of these patients to have normal LVEF by MUGA, and abnormal LVEF by GSPECT (Figures #4-6, vol. 2, pp. 220-223).

b. LV Wall Motion: Table #4.c.4 on the next page indicates the normal and abnormal readings for both SPECT by individual readers and MUGA by consensus, again presented as 2x2 tables (highlighted in gray) to compute sensitivity and specificity. The results also appear acceptable and comparable among the readers.

TABLE #4.c.4: 2x2 Tables of LV Wall Motion (Normal or Abnormal) for MUGA and GSPECT (Subject-level)

	Reader 1 GSPECT Assessment			Reader 2 GSPECT Assessment			Reader 3 GSPECT Assessment		
Consensus MUGA Assess.	Normal n	Abnormal n	Total n	Normal n	Abnormal n	Total	Normal n	Abnormal n	Total n
Normal	44	19	63	41	19	60	54	9	63
Abnormal	8	53	61	5	54	59	12	49	61
Total	52	72	124	46	73	119	66	58	124
Sensitivity	86.9%			91.5%			80.3%		
Specificity	69.8%			68.3%			85.7%		

(Ref. derived from Table 11.3.2.1, p. 229, vol. 2)

3. Additional efficacy analyses:

As indicated under Section #1.6, the *secondary efficacy endpoints* included 1) separate LVEF determinations by GSPECT for the stress Myoview images in those patients with LVEF <50% by MUGA, 2) LVEF determinations by GSPECT in those with LVEF >50% by MUGA; and 3) region-level wall motion assessment of the stress GSPECT images by the blinded readers. The cutoff of 50% for normal/abnormal LVEF was used to determine *sensitivity and specificity* for GSPECT in detecting an abnormality in global LV function. Sensitivity and specificity results are listed in Table #4.c.4. Although it was considered a primary endpoint by the applicant, *diagnostic accuracy,* influenced by the prevalence of LVEF or wall motion abnormality in the patient population, is not in of itself sufficient to support a claim of efficacy. Rather, the emphasis is on the "secondary" endpoints of *sensitivity/specificity* which are here reviewed as primary. Within the *abnormal* range of MUGA LVEF, the patients were subdivided into categories of <30%. 30-39% and 40-49% and MUGA and GSPECT values compared in "3x4 agreement tables" for each blinded reader. (Table #4.c.5 below). Agreement was best for those with severe LV dysfunction (LVEF <30%), with mean differences (MUGA LVEF - GSPECT LVEF) of –0.2 to -0.1%. For moderate LV dysfunction (LVEF 30-39%), MUGA values tended to exceed GSPECT (mean difference 7.5 to 7.6%). For mild LV dysfunction (LVEF 40-49%), MUGA values exceeded GSPECT by mean differences of 2.2 to 2.5%.

Table #4.c.5: Paired Differences of Measured LVEF Values within MUGA LVEF Groups

Reader 1						
MUGA LVEF (%)	**N**	**GSPECT LVEF (%)**				**Mean LVEF Difference (%)**
		<30	30-39	40-49	≥50	
<30	18	15 (83.3%)	2 (11.1%)	1 (5.6%)	0 (0.0%)	-0.1
30-39	17	9 (52.9%)	8 (47.1%)	0 (0.0%)	0 (0.0%)	7.5
40-49	22	2 (9.1%)	10 (45.5%)	3 (13.6%)	7 (31.8%)	2.5
≥50	70	17 (24.3%)			53 (75.7%)	Not provided
Reader 2						
MUGA LVEF (%)	**N**	**GSPECT LVEF (%)**				**Mean LVEF Difference (%)**
		<30	30-39	40-49	≥50	
<30	17	14 (82.4%)	2 (11.8%)	1 (5.9%)	0 (0.0%)	-0.2
30-39	16	8 (50.0%)	8 (50.0%)	0 (0.0%)	0 (0.0%)	7.6
40-49	21	2 (9.5%)	9 (42.9%)	3 (14.3%)	7 (33.3%)	2.0
≥50	67	14 (20.9%)			53 (79.1%)	Not provided
Reader 3						
MUGA LVEF (%)	**N**	**GSPECT LVEF (%)**				**Mean LVEF Difference (%)**
		<30	30-39	40-49	≥50	
<30	18	15 (83.3%)	2 (11.1%)	1 (5.6%)	0 (0.0%)	-0.1
30-39	17	9 (52.9%)	8 (47.1%)	1 (5.9%)	0 (0.0%)	7.5
40-49	21	2 (9.1%)	9 (40.9%)	4 (18.2%)	7 (31.8%)	2.2
≥50	70	16 (22.9%)			54 (77.1%)	Not provided

(Ref. derived from Tables 11.3.1.1 and 11.4.1.1, pp. 219 and 231, vol. 2)

TABLE #4.c.6: 2x2 Tables of LV Wall Motion (Normal or Abnormal) for MUGA and GSPECT (Anterior wall)

	Reader 1 GSPECT Assessment			Reader 2 GSPECT Assessment			Reader 3 GSPECT Assessment		
Consensus MUGA Assess.	Normal n	Abnormal n	Total n	Normal n	Abnormal n	Total n	Normal n	Abnormal n	Total n
Normal	68	11	79	61	15	76	75	4	79
Abnormal	21	24	45	4	39	43	15	30	45
Total	89	35	124	65	54	119	90	34	124
Sensitivity	53.3%			90.7%			53.4%		
Specificity	86.1%			80.3%			88.8%		

TABLE #4.c.7: 2x2 Tables of LV Wall Motion (Normal or Abnormal) for MUGA and GSPECT (Septal wall)

	Reader 1 GSPECT Assessment			Reader 2 GSPECT Assessment			Reader 3 GSPECT Assessment		
Consensus MUGA Assess.	Normal n	Abnormal n	Total n	Normal n	Abnormal n	Total n	Normal n	Abnormal n	Total n
Normal	62	7	69	55	11	66	61	8	69
Abnormal	42	13	55	13	40	53	20	35	61
Total	104	20	124	68	51	119	81	43	124
Sensitivity	23.6%			75.5%			63.6%		
Specificity	89.9%			83.3%			88.4%		

TABLE #4.c.8: 2x2 Tables of LV Wall Motion (Normal or Abnormal) for MUGA and GSPECT (Lateral wall)

	Reader 1 GSPECT Assessment			Reader 2 GSPECT Assessment			Reader 3 GSPECT Assessment		
Consensus MUGA Assess.	Normal n	Abnormal n	Total n	Normal n	Abnormal n	Total n	Normal n	Abnormal n	Total n
Normal	79	13	92	70	19	89	84	8	92
Abnormal	21	11	32	7	23	30	12	20	32
Total	100	24	124	77	42	119	96	28	124
Sensitivity	34.4%			76.7%			62.5%		
Specificity	85.9%			78.7%			91.3%		

TABLE #4.c.9: 2x2 Tables of LV Wall Motion (Normal or Abnormal) for MUGA and GSPECT (Inferior wall)

	Reader 1 GSPECT Assessment			Reader 2 GSPECT Assessment			Reader 3 GSPECT Assessment		
Consensus MUGA Assess.	Normal n	Abnormal n	Total n	Normal n	Abnormal n	Total n	Normal n	Abnormal n	Total n
Normal	71	18	89	54	32	86	76	13	89
Abnormal	13	22	35	4	29	33	6	29	35
Total	84	40	124	58	61	119	82	42	124
Sensitivity	47.6%			87.9%			82.9%		
Specificity	71.5%			62.8%			85.4%		

TABLE #4.c.10: 2x2 Tables of LV Wall Motion (Normal or Abnormal) for MUGA and GSPECT (Apical wall)

	Reader 1 GSPECT Assessment			Reader 2 GSPECT Assessment			Reader 3 GSPECT Assessment		
Consensus MUGA Assess.	Normal n	Abnormal n	Total n	Normal n	Abnormal n	Total	Normal n	Abnormal n	Total n
Normal	52	20	72	55	14	69	68	4	72
Abnormal	14	38	52	9	41	50	14	38	52
Total	66	58	124	64	55	119	82	42	124
Sensitivity	73.1%			82.0%			73.1%		
Specificity	72.2%			79.7%			94.4%		

(Ref. derived from Tables 11.4.2.1 to 11.4.2.5, pp. 232-236, vol. 2)

Wall motion was also analyzed on a *segmental* level (anterior, lateral, septal, inferior, apical) and compared in 2x2 tables (previous page) for each segment and each reader. Results were reported as sensitivity and specificity in the same way as those for subject-level analyses of wall motion. Tables #4.c.6 - #4.c.10 present the 2x2 results for each segment of the LV as well as sensitivity/specificity for wall motion abnormalities in each segment.

A look at these tables shows Readers 1 and 3 to have poor *sensitivity* for abnormal wall motion in the anterior and septal segments (as low as 23.6% for Reader 1 septum). Reader 1 performed poorly for the lateral wall as well (34.4% sensitivity), and only fair for the inferior wall (62.9%). Otherwise, sensitivity for detecting apical and inferior wall abnormalities was good amongst the 3 readers (range ——— %) All blinded readers performed well with respect to *specificity*, and assessment of the apex appeared to be the most consistent.

Analyses of *inter-* and *intra-reader variability* with respect to subject-level wall motion assessments were also made. The kappa statistics and proportion of agreement were reported. Table #4.c.11 below indicates the inter-reader variability for global wall motion.

TABLE #4.c.11: Inter-reader Agreement for Subject-level Wall Motion Assessment

Observer Pair	Kappa (κ)	Proportion of Agreement of Normality	Proportion of Agreement of Abnormality
Reader 1 – Reader 2	0.61	0.63	0.72
Reader 2 – Reader 3	0.63	0.68	0.70
Reader 1 – Reader 3	0.56	0.61	0.65

(Ref. derived from Table 11.6.1, p. 237, vol. 2)

To evaluate *intra*-reader variability, 10% of the 140 GSPECT images were read twice by each of the 3 blinded readers. One of the 14 studies (7.1%) was re-classified on the second reading by each of the readers. Of the 3 changes, 2 were from abnormal to normal wall motion. The time interval between reads was not specified, in the protocol, study report or individual patient data listings.

Inter- and intra-reader agreement analysis was not applied to LVEF, as ejection fraction for GSPECT is computed by an automated software program, and inter-reader variation only occurs if one reader decides to recalculate the LVEF and another does not. Of the 140 GSPECT studies, 4 (2.6%) were re-calculated by Reader 3 and none by the other two readers.

3. Results: Study MYO-303:

3:1. Demographics and Baseline Characteristics

A total of 191 patients at 9 U.S. centers enrolled in MYO-303. Four patients were withdrawn prior to Myoview, leaving a safety population of 187. Four were withdrawn due to absence of stress, 1 due to the use of pharmacologic stress; 1 did not have a gated SPECT, leaving 181 to have an exercise stress GSPECT. Three GSPECT images were removed due to core lab error or suboptimal image quality. MUGA was acquired in 175, of which 1 was suboptimal. The remaining 174 comprise the efficacy population.

Among the 191 patients, 160 (83.8%) had a cardiovascular history; heart failure was present in 35 (18.3%); angina pectoris in 54 (28.3%); prior MI in 64 (33.5%); prior CABG in 31 (16.2%) and prior PTCA in 56 (29.3%). Demographics for the enrolled population are summarized in Table #4.c.12 below. The percentage of females is 8.5% higher than in MYO-301.

TABLE #4.c.12: Demographic Information: Study MYO-303

Demographic Parameter		Patients (191)
Sex:	Male	118 (61.8%)
	Female	73 (38.2%)
Age (years):	Mean ± SD	59.9± 12.7
	Range	20 – 88 years
	<65	108 (56.5%)
	65 – 80	77 (40.3%)
	>80	6 (3.1%)
Race:	White	162 (84.8%)
	Black	26 (13.6%)
	Other	3 (1.6%)
Weight (lb.)	Mean	86.8 ± 19.8
	Range	47 – 163 kg
Height (in.)	Mean	171 ± 10.1
	Range	147 – 193 cm

(Ref. vol. 13, p. 49)

3:2. Dosage and Administration

In Study MYO-303, 183 patients received both doses of, Myoview, and 175 also underwent a satisfactory MUGA examination. Two patients received only 1 dose of Myoview (stress). For the resting images, a large majority (151) received the low Myoview dose (mean 11.2 mCi, range ——— mCi). Thirty-six patients received the high rest Myoview dose (mean of 17.4 mCi, range ——— mCi). For stress images in 183 patients, the mean dose was 22.6 mCi, range ——— mCi. As in MYO-301, for the MUGA study, the range of ——— doses among the 175 patients was specified as 15-20 mCi, however, individual doses were not reported in summary tables or patient data listings.

3:3. Efficacy Results: Study MYO-303

1. Datasets analyzed: From the 183 patients who underwent rest and stress Myoview GSPECT and 175 undergoing MUGA, a number of patients were eliminated from the efficacy analysis due to suboptimal MUGA (mostly from poor RBC labeling) or GSPECT exams as read by the blinded readers (3 readers for the GSPECT images and 3 readers for the MUGA scans). Table #4.c.13 below indicates the denominator of remaining evaluable patients for each reader of the GSPECT images:

TABLE #4.c.13: Evaluable Patients: Study MYO-303

ENDPOINT	Reader 1	Reader 2	Reader 3
LVEF	169	169	168
Wall Motion	170	170	169

(Ref. derived from Figure 3, vol. 13, p. 53)

2. Efficacy analyses: sensitivity, specificity

The results of comparing the Tc-99m tetrofosmin gated images against the truth standard (MUGA) were reported for LV ejection fraction (Endpoint 1) and global LV wall motion (Endpoint 2). LVEF values and wall motion were scored as in Study MYO-301.

a. LVEF: Table #4.c.14 below indicates the normal and abnormal readings for both SPECT by individual readers and MUGA by consensus, to compute *sensitivity* and *specificity.* As in MYO-301, the results appear acceptable and comparable among the readers.

TABLE #4.c.14: 2x2 Tables of LVEF (Normal or Abnormal) for MUGA (Consensus) and GSPECT (3 blinded readers)

	Reader 1 GSPECT Assessment			Reader 2 GSPECT Assessment			Reader 3 GSPECT Assessment		
Consensus MUGA Assess.	Normal n	Abnormal n	Total n	Normal n	Abnormal n	Total n	Normal n	Abnormal n	Total n
Normal	85	15	100	85	16	101	84	16	100
Abnormal	13	56	69	13	55	68	13	55	68
Total	98	71	169	98	71	169	97	71	168
Sensitivity	81.2%			80.9%			80.9%		
Specificity	85.0%			84.2%			84.0%		

(Ref. derived from Table 11.3.1.1, p. 57, vol. 13)

As in MYO-301, reporting of numerical LVEF values was in the form of scatter plots and Bland-Altman plots of consensus MUGA LVEF vs. GSPECT LVEF for each reader. For the 3 readers, both scatter and Bland-Altman plots were very similar, and, as in MYO-301, there was a tendency for GSPECT to underestimate LVEF at low values. At high LVEF values, GSPECT tended to overestimate the LVEF, somewhat more than in the other study. The applicant's explanation of underestimation of end-systolic LV volume (and therefore too high an LVEF) in small hearts as being due to technical factors is reasonable. (References #35: Evereart et. al. and #36: Ford et. al., vol. 29, pp. 225-244) As in MYO-301, the use of 8 frames rather than 16 for ECG gating of SPECT images offers a good explanation for underestimating LVEF. Also, as in MYO-301, the GSPECT was done 15-45 minutes after exercise and MUGA was done at rest. Therefore, the GSPECT LVEF values may be *lower* post-stress in CAD patients experiencing ischemia and consequent LV dysfunction.

b. LV Wall Motion: As in MYO-301, Table #4.c.15 below indicates the normal and abnormal readings for both SPECT by individual readers and MUGA by consensus, sensitivity, specificity. The results also appear acceptable and comparable among the readers. For Readers 1 and 2, specificities are better than in MYO-301; sensitivity is slightly lower for Reader 2; the results are otherwise comparable to the other study.

TABLE #4.c.15: 2x2 Tables of LV Wall Motion (Normal or Abnormal) for MUGA and GSPECT (Subject-level)

	Reader 1 GSPECT Assessment			Reader 2 GSPECT Assessment			Reader 3 GSPECT Assessment		
Consensus MUGA Assess.	Normal n	Abnormal n	Total n	Normal n	Abnormal n	Total n	Normal n	Abnormal n	Total n
Normal	79	25	104	87	18	105	85	19	104
Abnormal	8	54	62	10	51	61	10	51	61
Total	87	79	166	97	69	166	95	70	165
Sensitivity	87.1%			83.6%			83.6%		
Specificity	76.0%			82.9%			81.7%		

(Ref. derived from Table 11.3.2.1, p. 67, vol. 13)

Patients whose LVEF values were abnormal on one modality and normal on the other, and whose quantitative values differed by 10% or more were considered "outliers". For Reader 1, there were 21 out of 169 patients (12.4%); for Reader 2, 22 out of 169 patients (13.0%) and for Reader 3, 23 out of 170 patients (13.6%). These percentages are comparable to those in MYO-301. The scatterplots showed most of these patients to have higher LVEF values as determined by GSPECT (Figures #4-6, vol. 13, pp. 58-60).

3. Additional efficacy analyses:

As in MYO-301, within the abnormal range of MUGA LVEF, patients were subdivided into categories of <30%, 30-39% and 40-49%; and MUGA and GSPECT values compared in "3x4 agreement tables" for each blinded reader. (Table #4.c.16 below). For those with severe LV dysfunction (LVEF <30%), the mean MUGA LVEF values exceeded GSPECT values by 1.7 to 3.1%. For moderate LV dysfunction (LVEF 30-39%), the MUGA LVEF values exceeded GSPECT values by 3.3 to 4.6%. For mild LV dysfunction (LVEF 40-49%), GSPECT LVEF values exceeded MUGA by mean values of 2.5 to 3.3%.

Comparison of these results with the corresponding data from MYO-301 shows the correlation to be better for LVEF's in the 30 to 39% range, but not as close for LVEF's below 30% (in MYO-301, MUGA and GSPECT LVEF values in patients with severe dysfunction were nearly identical). For mild LV dysfunction (LVEF 40-49%), the differences are slightly greater for this study, but in the opposite direction. The applicant was not able to explain the opposite trend for those with mild LV dysfunction. If one pools the results for the 6 blinded readers in both studies, the LVEF differences for those with mild dysfunction virtually cancel each other out (Table #9.2.1.2.1 in the ISE: vol. 27, p. 56). Given that the accepted margin of error for LVEF determination by MUGA in clinical practice is 5%, this reviewer considers these deviations entirely acceptable.

Table =4.c.16: Paired Differences of Measured LVEF Values within MUGA LVEF Groups

Reader 1						
MUGA LVEF (%)	**N**	**GSPECT LVEF (%)**				**Mean LVEF Difference (%)**
		<30	30-39	40-49	≥50	
<30	12	11 (91.7%)	1 (8.3%)	0 (0.0%)	0 (0.0%)	2.5
30-39	22	9 (40.9%)	11 (50.0%)	2 (9.1%)	0 (0.0%)	3.3
40-49	35	2 (5.7%)	5 (14.3%)	15 (42.9%)	13 (37.1%)	-3.3
≥50	100	15 (15.0%)			85 (85.0%)	Not provided
Reader 2						
MUGA LVEF (%)	**N**	**GSPECT LVEF (%)**				**Mean LVEF Difference (%)**
		<30	30-39	40-49	≥50	
<30	11	10 (90.9%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	1.7
30-39	22	9 (40.9%)	11 (50.0%)	2 (9.1%)	0 (0.0%)	3.3
40-49	35	2 (5.7%)	5 (14.3%)	15 (42.9%)	13 (37.1%)	-3.3
≥50	101	16 (15.8%)			85 (84.2%)	Not provided
Reader 3						
MUGA LVEF (%)	**N**	**GSPECT LVEF (%)**				**Mean LVEF Difference (%)**
		<30	30-39	40-49	≥50	
<30	12	11 (91.7%)	1 (8.3%)	0 (0.0%)	0 (0.0%)	3.1
30-39	21	10 (47.6%)	10 (47.6%)	1 (4.8%)	0 (0.0%)	4.6
40-49	35	4 (11.4%)	4 (11.4%)	14 (40.0%)	13 (37.1%)	-2.5
≥50	100	16 (16.0%)			84 (84.0%)	Not provided

(Ref. derived from Table 11.4.1.1, p. 69, vol. 13)

As in MYO-301, results for wall motion on a segmental level were reported as *sensitivity* and *specificity* in the same way as were those for subject-level analyses. Tables #4.c.17 to #4.c.21 on the next page present the 2x2 results for each segment of the LV as well as sensitivity/ specificity for wall motion abnormalities in each segment.

TABLE #4.c.17: 2x2 Tables of LV Wall Motion (Normal or Abnormal) for MUGA and GSPECT (Anterior wall)

	Reader 1 GSPECT Assessment			Reader 2 GSPECT Assessment			Reader 3 GSPECT Assessment		
Consensus MUGA Assess.	Normal n	Abnormal n	Total n	Normal n	Abnormal n	Total n	Normal n	Abnormal n	Total n
Normal	108	22	130	122	8	130	114	16	130
Abnormal	25	26	31	3	28	31	4	27	31
Total	113	48	161	125	36	161	118	43	161
Sensitivity	83.9%			90.3%			87.1%		
Specificity	83.1%			93.9%			87.7%		

TABLE #4.c.18: 2x2 Tables of LV Wall Motion (Normal or Abnormal) for MUGA and GSPECT (Septal wall)

	Reader 1 GSPECT Assessment			Reader 2 GSPECT Assessment			Reader 3 GSPECT Assessment		
Consensus MUGA Assess.	Normal n	Abnormal n	Total n	Normal n	Abnormal n	Total n	Normal n	Abnormal n	Total n
Normal	105	23	128	105	24	129	98	29	127
Abnormal	8	34	42	11	30	41	6	36	42
Total	113	57	170	116	54	170	104	65	169
Sensitivity	81.0%			73.2%			85.7%		
Specificity	82.0%			81.4%			77.2%		

TABLE #4.c.19: 2x2 Tables of LV Wall Motion (Normal or Abnormal) for MUGA and GSPECT (Lateral wall)

	Reader 1 GSPECT Assessment			Reader 2 GSPECT Assessment			Reader 3 GSPECT Assessment		
Consensus MUGA Assess.	Normal n	Abnormal n	Total n	Normal n	Abnormal n	Total n	Normal n	Abnormal n	Total n
Normal	125	17	142	130	13	143	127	14	141
Abnormal	4	24	28	5	22	27	6	22	28
Total	129	41	170	135	35	170	133	36	169
Sensitivity	85.7%			81.5%			78.6%		
Specificity	88.0%			90.9%			90.1%		

TABLE #4.c.20: 2x2 Tables of LV Wall Motion (Normal or Abnormal) for MUGA and GSPECT (Inferior wall)

	Reader 1 GSPECT Assessment			Reader 2 GSPECT Assessment			Reader 3 GSPECT Assessment		
Consensus MUGA Assess.	Normal n	Abnormal n	Total n	Normal n	Abnormal n	Total n	Normal n	Abnormal n	Total n
Normal	97	14	111	103	9	112	102	9	111
Abnormal	10	43	53	10	42	52	12	40	52
Total	107	57	164	113	51	164	114	49	163
Sensitivity	81.1%			80.8%			76.9%		
Specificity	87.4%			92.0%			91.9%		

TABLE #4.c.21: 2x2 Tables of LV Wall Motion (Normal or Abnormal) for MUGA and GSPECT (Apical wall)

	Reader 1 GSPECT Assessment			Reader 2 GSPECT Assessment			Reader 3 GSPECT Assessment		
Consensus MUGA Assess.	Normal n	Abnormal n	Total n	Normal n	Abnormal n	Total n	Normal n	Abnormal n	Total n
Normal	99	18	117	104	14	118	104	13	117
Abnormal	7	37	44	7	36	43	7	37	44
Total	106	55	161	111	50	161	111	50	161
Sensitivity	84.1%			83.7%			84.1%		
Specificity	84.6%			88.1%			88.9%		

(Ref. derived from Tables 11.4.2.1 - 11.4.2.5, pp. 70-74, vol. 13)

A look at these tables shows all readers to have good sensitivity and specificity for abnormal wall motion in all five myocardial segments (the lowest value was 76.9% for Reader 3 inferior wall). When compared to Study MYO-301, these results are far more consistent, particularly for sensitivity in all segments but the apical wall of the LV.

As in MYO-301, analyses of inter- and intra-reader variability in subject-level wall motion assessments were made. Kappa statistics and proportion of agreement were again used as measures. Table #4.c.22 below presents inter-reader variability for global wall motion. The kappa values show inter-reader agreement to be better than in MYO-301, and consistent with the better overall consistency of performance among the readers in this study.

TABLE #4.c.22: Inter-reader Agreement for Subject-level Wall Motion Assessment

Observer Pair	Kappa (κ)	Proportion of Agreement of Normality	Proportion of Agreement of Abnormality
Reader 1 – Reader 2	0.76	0.81	0.76
Reader 2 – Reader 3	0.80	0.84	0.80
Reader 1 – Reader 3	0.77	0.83	0.76

(Ref. derived from Table 11.6.1.1, p. 75, vol. 13)

To evaluate *intra*-reader variability, 10% (18) of the 178 GSPECT images were read twice by each of the 3 blinded readers. One of the 18 studies (5.6%) was re-classified on the second reading by Reader #2, whose change was from normal to abnormal wall motion. None of the other reads was re-classified. As in MYO-301, the time interval between reads was not specified, in the protocol, study report or individual patient data listings.

As in MYO-301, inter- and intra-reader agreement analysis was not applied to LVEF, as ejection fraction for GSPECT is computed by an automated software program, and inter-reader variation only occurs if one reader decides to recalculate the LVEF and another does not. Of the 178 GSPECT studies, 1 (0.6%) was re-calculated by Reader 1, none (0.0%) by Reader 2 and 15 (8.4%) by Reader 3. Given the otherwise consistent reads among the 3 blinded readers in MYO-303, the relatively high number of re-calculations by Reader 3 is surprising.

4. Reviewer's discussion, issues of concern and conclusions

The two elements of left ventricular function evaluated in MYO-301 and 303 were LV ejection fraction and regional wall motion. The *primary* endpoints addressed LV ejection fraction (*accuracy*) and *subject-level* wall motion abnormalities; the *secondary* endpoints addressed discriminating normal from abnormal LVEF (*sensitivity* and *specificity*) and specific (*regional*) wall motion abnormalities. Since the policy of the Division is to emphasize sensitivity and specificity rather than accuracy, the secondary endpoints for the two studies have been reviewed as though they were primary.

Equilibrium gated cardiac blood pool imaging (MUGA), using Tc-99m tagged RBC, evaluates function by imaging the blood pool *inside* the LV chamber rather than the LV wall itself. In May of 2000, this method was suggested to the applicant by the Division as a truth standard rather than ——— which has not yet been approved by the FDA. For Myoview perfusion imaging, the only way to visualize the cardiac blood pool in a similar way as the MUGA truth standard is to do "first-pass" techniques, which require special high-sensitivity gamma camera equipment. Due to this limitation, the applicant has elected to use the "equilibrium" myocardial perfusion images, which visualize the cardiac wall rather than the cardiac blood pool. Since the Myoview images and the truth standard are essentially looking at "opposite sides" of the endocardial border to provide the same information, the potential for discrepancies in results is increased. The use of equilibrium GSPECT was agreed upon in June of 2001 when the applicant explained that first-pass imaging would not be practical due to the high-sensitivity gamma cameras needed.

Given the above limitations, the overall sensitivity/specificity of GSPECT for detecting left ventricular dysfunction (LVEF <50% and wall motion abnormality) and the levels of concordance between MUGA and GSPECT shown in both studies are surprisingly good. The tendency for GSPECT to underestimate LVEF at low values is explained well: "truncation" of the time-activity curve for GSPECT by 8-frame gating, and the possibility of post-stress "stunning" reducing myocardial contraction during the stress GSPECT acquisition. However, the applicant should analyze LVEF values in the subgroup of patients who had evidence of ischemia during stress (angina, ST-depression, myocardial perfusion defect on Myoview) to further substantiate the theory of "stunning" as an explanation for lower stress LVEF values. A comparison of resting MUGA with resting GSPECT LVEF would eliminate the "stunning" factor altogether. For patients with normal to high LVEF values (especially women with small LV chamber size) the potential for GSPECT to underestimate end-systolic volume (and overestimate LVEF) exists. In the opinion of this reviewer, the applicant has provided a reasonable explanation for this: technical limitations in the imaging software and hardware, as described in two articles (References #35: Evereart et. al. and #36: Ford et. al., vol. 29, pp. 225-244) in the literature.

In the opinion of this reviewer, both of these studies are of a satisfactory design and have demonstrated an acceptable level of efficacy given the inherent physical limitations and differences of MUGA and GSPECT as methods for evaluating LV function. Although some concerns have arisen, these do little to compromise the overall supportive value of the studies.

To obtain both myocardial perfusion and LV function information from the same radionuclide study is a goal which is reasonable, both in terms of increased efficiency and reduced cost. As long as the physician managing the patient is aware of the limitations of GSPECT discussed above, the functional assessment of the LV obtained using this method has been shown to be sufficiently reliable to achieve this goal.

D.4.d. Efficacy Review of Submitted Articles from the Literature

1. Introduction and Literature Article Selection Process

In NDA #20,372 SEI 013 (vol. 26), the applicant has provided 22 articles (Table 4.d.1) from the published literature on Myoview GSPECT; a MEDLINE search was conducted, using key-words to obtain titles and abstracts. Review of the Integrated Summary of Efficacy has shown that the applicant did not include these articles as an integral part of the clinical data intended to support the GSPECT indication. Despite this, selected articles were reviewed for their potential supportive value. The methods of selection and step-wise elimination of articles is described in the following paragraphs. Articles provided in the submission cover a 5-year time period (1996-2001), the time during which GSPECT imaging of myocardial perfusion agents has been in clinical use. All articles were written in English and represented studies in humans.

Only articles comparing Myoview (not Tc-99m sestamibi) GSPECT with a comparator or truth standard with respect to global and/or regional LV function were considered by this reviewer for their potential to support the efficacy claim. These 15 articles are listed in Table #4.d.2. Twelve of these were summarized by the applicant (pp. 5-13, vol. 26).

These articles were reviewed according to criteria established in the FDA *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products* of May 1998 (Clinical 6). According to the *Guidance*, the following were some of the features that were considered relevant for this review (page 19 of the *Guidance*):

- Multicenter studies using different investigators
- Protocol design described and prospectively studied
- Clear and appropriate endpoints, objectively assessed and independent of investigator judgment
- Inclusion and reporting results of a safety assessment
- Specified purpose, with high level of detail in report, statistical plans and analytical methods
- A full accounting of all enrolled patients/subjects, clearly defined study population
- Blinded reads (preferably independent)
- Consistent findings across studies and robust results yielding a consistent conclusion of efficacy without need for *post-hoc* analyses or reduced datasets (such as "evaluable" subjects)
- Use of a truth standard or comparator against which the imaging modality (and drug) would be compared (radionuclide ventriculography, left ventriculography, echo or MRI)
- Conduct of studies using groups with properly documented operating procedures and a history of implementing such procedures effectively.

In addition, the following features were also sought:

- $N \geq 25$ subjects
- No dual-isotope rest/stress studies (i.e. Tl-201 and Tc-labelled perfusion agent)
- No "atypical" stress techniques (i.e. concurrent exercise and pharmacologic stress)

The 22 submitted articles are listed in Table #4.d.1 on the next page.

Table #4.d.1: Submitted Literature Articles: Myoview SEI 013

Article # *	Author, date	# of Subjects	Multi-center	Pro-spective	Objective endpoints	Safety assess.	Blinded readers	Stats. plan	Acct. of subjects	Consist. findings	Compa-rator
1	Abe et. al. 2000	229 patients	-	+	+	-	+	+	-	+	Contrast LVG
2	Atsma et. al. 2000	74 patients	+	+	+	-	+	+	-	+	Contrast LVG
3	Ban et. al. 2000	20 patients	-	+	+	-	+	+	+	+	Contrast LVG
4	Bavelaar-Croon et. al. 2001	75 patients	-	-	+	-	-	+	-	NA	-
5	Bavelaar-Croon et. al. 2001	81 patients	-	+	+	-	-	+	-	NA	-
6	Chua et. al. 2000	77 patients	-	+	+	-	+	+	-	+	RVG Echo
7	Cwajg et. al. 1999	109 patients	-	+	+	-	-	+	-	+	Echo
8	Everaert et. al. 1997	40 patients	-	+	+	-	-	+	-	+	RVG
9	Everaert et. al. 1996	50 patients	+	+	+	-	-	+	-	+	RVG
10	Gunning et. al. 1996	28 patients	-	+	+	-	+	+	-	+	MRI
11	Kumita et. al. 1999	8 healthy	-	+	-	-	-	+	-	NA	-
12	Kumita et. al. 1998	25 patients	-	-	+	-	-	+	-	NA	-
13	Nakajima et. al. 1997	29 patients	+	-	+	-	-	+	-	+	RVG LVG
14	Paul et. al. 2000	15 patients	-	+	+	-	-	+	-	+	RVG SPECT
15	Toba et. al. 2000	49 patients	-	+	+	-	-	+	-	+	Contrast LVG
16	Vaduganathan et. al. 1999	25 patients	-	+	+	-	+	+	-	+	MRI
17	Wahba et. al. Feb. 2001	25 patients	-	+	+	-	+	+	-	+	Echo
18	Wahba et. al. Apr. 2001	26 patients	-	+	+	-	+	+	-	+	Contrast LVG
19	Wahba et. al. June 2001	21 patients	-	+	+	-	+	+	-	+	MRI
20	Wright et. al. 2001	71 patients	+	+	+	-	-	+	-	-	RVG
21	Yoshioka et. al. 1999	21 patients	-	+	+	-	-	+	+	+	FPRVG LVG
22	Zuber et. al. 2000	55 patients	-	+	+	-	-	+	-	+	Echo

(Ref. derived from list of articles, pp. 19-21, vol. 26 of submission) NA = not applicable

2. Preliminary Selection of Literature Articles

The table above clearly demonstrates that none of the articles met all of the Agency criteria. As indicated above, a truth standard or comparator was used in only 18 of the studies. Three papers were eliminated: #6 because 49 of 77 patients were given Tc-99m sestamibi, #7 because of use of dual-isotope rest/stress imaging and #13 because of the use of gated planar Myoview imaging rather than SPECT (#13). The remaining 15 articles are listed in Table 4.d.2 on the next page, with dose of Myoview and endpoints evaluated.

Table #4.d.2: Preliminary Selection of Literature Articles and Agreement Results with Comparators: Efficacy

Article #	# of Patients	Author, date	Images evaluated and dose			Endpoints evaluated			Overall Agreement Results with Comparator (%, r-values or kappa)
			Rest exam	Exercise stress	Pharm. stress	LVEF	LV Volumes	LV Wall Motion	
1	229	Abe et. al. 2000	9.5 mCi			+	+	+	r = 0.78 for LVEF r = 0.94 for wall motion
2*	74	Atsma et. al. 2000	6.8 mCi or 13.5 mCi	20.3 mCi	20.3 mCi	+	+	+	r = 0.92 for LVEF κ = 0.76 for wall motion
3	20	Ban et. al. 2000	20 mCi			+	+	+	r = 0.63 for LVEF r = 0.40 for wall motion
8	40	Everaert et. al. 1997	25 mCi			+	+		r = 0.93 for LVEF, 0.98 for ESV, 0.97 for EDV
9	50	Everaert et. al. 1996	25 mCi			+			r = 0.93 for 8-frame LVEF
10*	28	Gunning et. al. 1996	20.3 mCi	Combined exercise and adenosine, not evaluated				+	78% agreement κ = 0.66 for wall motion
14	15	Paul et. al. 2000	20 mCi			+	+		r = 0.97 for LVEF, 0.99 for ESV, 0.99 for EDV
15	49	Toba et. al. 2000	20 mCi			+	+		r = 0.72 for Emory LVEF r = 0.69 for Cedars LVEF
16*	25	Vaduganathan et. al. 1999	25-30 mCi			+	+	+	r = 0.93 for LVEF κ = 0.66 for wall motion
17*	25	Wahba et. al. Feb. 2001	6.8 mCi or 13.5 mCi	20.3 mCi	20.3 mCi			+	80% agreement κ = 0.40 for wall motion
18*	26	Wahba et. al. Apr. 2001	13.5 mCi	13.5 mCi	13.5 mCi			+	80% agreement κ = 0.67 for wall motion
19	21	Wahba et. al. June 2001	6.8 mCi or 13.5 mCi	20.3 mCi	20.3 mCi			+	84% agreement κ = 0.72 for wall motion.
20	71	Wright et. al. 2001	19.6 mCi			+			r = 0.81 for 8-frame LVEF r = 0.82 for 16-frame LVEF
21	21	Yoshioka et. al. 1999	20 mCi			+	+		r = 0.91 for LVEF, 0.72 for ESV, 0.61 for EDV
22	55	Zuber et. al. 2000	70.3-13.5 mCi	Combined exercise and adenosine, not evaluated		+	+		r = 0.67 for LVEF, 0.86 for ESV, 0.86 for EDV

(Ref. derived from review of articles, vol. 26 of submission)

Of the 15 articles, 11 evaluated *global* LV function (LVEF and/or end-systolic and diastolic volumes), 4 of these compared Myoview GSPECT with radionuclide ventriculography, 5 with contrast left ventriculography, 1 with cine MRI and 2 with echocardiography. *Regional* LV function (wall thickening and motion) was evaluated in 8 articles, comparing GSPECT to contrast left ventriculography in 4, to cine MRI in 3 and echocardiography in 1. Six studies included stress Myoview imaging; all used either pharmacologic (adenosine) or exercise stress, but 2 of these used a combination of low-level exercise and pharmacologic stress which is not approved by FDA at this time. The Myoview doses were all within the range of approved doses for rest-only or 1- or 2-day rest/stress protocols for evaluating myocardial perfusion. Eleven of the 15 studies had a sample size of 25 or more; 8 were indicated to include a blinded reading of images. All of the 15 studies enrolled patients with heart disease. A look at the overall agreement results between GSPECT and comparator modalities (contrast LVG, first-pass and equilibrium RVG, echo, cine MRI) shows a range of correlation coefficients (r-values) of 63% to 97% for LVEF and a wider range for regional wall motion scores (r = 40% to 94%; κ = 0.40 to 0.72).

To narrow the choices down to articles with the greatest potential for supporting the claim, this reviewer selected 5 papers (#2, 10, 16, 17, 18) from the above list which investigated 25 or more patients and had at least 5 other positive characteristics as listed in Table #4.d.1. These papers are briefly summarized in the following pages.

3. Review of Selected Literature Articles

Article #2: Atsma et. al. 2000. *International Journal of Cardiac Imaging,* vol. 16, pp. 28-34

Title: "Good correlation between gated single-photon emission computed myocardial tomography and contrast ventriculography in the assessment of global and regional left ventricular function"

Purpose of study: To determine the reliability of measured LVEF values and wall motion analysis provided by ECG-gated quantitative Tc-99m tetrofosmin SPECT perfusion images by comparison with contrast left ventriculography.

Subjects and Methods: This study prospectively evaluated 74 patients with undiagnosed chest pain of whom 27 had sustained a previous myocardial infarction. All patients underwent gated Myoview SPECT at rest and during pharmacologic or exercise stress (57 for a 2-day protocol at 13.5 mCi/day and 17 for a 1-day protocol with 6.8 mCi at rest and 20.3 mCi at stress). LV angiography was performed within 3 months without changes in cardiac status.

Data Processing: SPECT images were acquired using a 360 degree arc with 90 stops of 35 seconds each. Reconstructed transaxial images were formatted into 16 frames per cardiac cycle, and LV volumes and LVEF computed using operator-independent commercial software (QGS by Germano et. al). for the LV angiograms, ES and ED volumes were computed using manually traced ROI's, which were also used to assess regional wall motion. To compare wall motion in each segment, SPECT 3-dimensional images were re-oriented and displayed to correspond to the RAO and LAO angiographic views.

Statistical Methods: LVEF and ventricular volumes from the SPECT images were compared to those for the LV angio through linear regression analysis, the paired Student T-test and generation of Bland-Altman plots to look for trends in the LVEF difference for the two modalities at each LVEF value. For wall motion scores, the modalities were compared using 4x4 agreement tables and kappa statistics.

Summary of Results and Findings: LVEF as measured by angio ranged from 20% to 90% and by GSPECT from 15% to 87%. The R-value was 0.94, $p < 0.0001$. To separate out patients in whom reduced uptake of Myoview might hamper evaluation of segmental function, patients with a prior MI were studied separately; for these 27 patients, the corresponding R was 0.89 and $p < 0.0001$. The Bland-Altman graph showed no systemic trend for the in the difference between LVEF values for each modality; in particular, no underestimation of LVEF was seen at lower EF values as was seen in the pivotal studies MYO-301 and 303.

Conclusions: Overall, the results of this study show an excellent correlation between GSPECT and angiography, both for global and regional LV function. The most likely explanation for the lack of LVEF underestimation seen in patients with poor function seen in this study and the presence of this problem in the pivotal trials is the use of 16-frame gating here and 8-frame gating in the pivotals. Concerns raised by poor uptake in hypoperfused segments of myocardium making assessment of wall motion difficult are not substantiated by the continued good agreement with angiography for the post-MI subgroup of 27 patients.

Article # 10: Gunning et. al. 1999. *Journal of Nuclear Medicine,* vol. 38, pp. 438-442

Title: "Gated technetium 99m tetrofosmin SPECT and cine MRI to assess left ventricular function"

Purpose of study: To compare assessments of myocardial wall motion and thickening obtained using Myoview GSPECT with those from cine MRI in patients referred for routine myocardial perfusion scintigraphy.

Subjects and Methods: This study prospectively evaluated 28 patients referred for evaluation of myocardial perfusion. Fifteen had previously documented CAD and 12 a prior myocardial infarction. All patients underwent gated Myoview SPECT at rest and during pharmacologic (adenosine) stress combined with submaximal exercise for a 1-day protocol with 6.8 mCi of Myoview at rest and 20.3 mCi at stress. Resting cine MRI of the heart with ECG triggering was done in all subjects (timeframe not specified) to serve as a comparator for the resting GSPECT wall motion and wall thickening assessments. Only the resting GSPECT images were compared with MRI.

Data Processing: SPECT images were acquired using a 180 degree arc with 64 stops of 50 seconds each. Reconstructed trans-axial images were formatted into 16 frames per cardiac cycle; LV volumes and LVEF were computed using operator-independent commercial software. The LVEF values were not compared to MRI but were used to stratify subgroups of patients with LVEF <35% and >35%. For the cine MRI, ES and ED volumes were computed using manually traced ROI's, which were also used to assess endocardial wall motion, myocardial thickness and systolic thickening. Wall motion and thickening were reported as a score for each of 9 ventricular segments (a 6-point scale for motion and 5-point scale for thickening). To compare these parameters in each segment, SPECT and MRI images were re-oriented and displayed in corresponding short axis and horizontal/vertical long axes.

Statistical Methods: For wall motion scores, the modalities were compared using kappa statistics. Segments judged as "unclassifiable" were excluded from the analysis. Analyses were performed for the group as a whole and subgroups of patients with normal LV function and patients with abnormal regional function with LVEF <35% and LVEF >35%. Within these groups, inter- and intra-observer agreement was also evaluated.

Summary of Results and Findings: A total of 252 myocardial segments were evaluated, of which 15 could not be classified by GSPECT due to insufficient uptake of Myoview. For wall motion, agreement in scores for well-perfused segments was generally better than poorly perfused segments. Within the study populations, segmental kappa values for patients without LV dysfunction were all 1.0 while those for LV dysfunction patients were 0.54 and 0.39 for wall motion and thickening, respectively in patients whose LVEF >35% and 0.48 and 0.41 for wall motion and thickening, in patients whose LVEF <35%.

Conclusions: Though the group of patients is much smaller than in Reference #2, the results again show an excellent overall correlation of wall motion scores between GSPECT and the comparator, which in this case is gated MRI. Regional assessment of wall motion and thickening produced kappas of 0.74 and 0.80 for inter-observer and 0.85 and 0.84 for intra-observer agreement, respectively, for global and regional LV function. Unlike in Reference #2, poor uptake in hypoperfused segments of myocardium resulted in a reduction of the agreement scores and kappa values for wall motion and thickening scores in these segments.

Article # 16: Vaduganathan et. al. 1998. *Journal of Nuclear Cardiology,* vol. 6, pp. 3-10

Title: "Evaluation of left ventricular wall motion, volumes and ejection fraction by gated myocardial tomography with technetium-99m tetrofosmin: a comparison with cine magnetic resonance imaging"

Purpose of study: To compare assessments of myocardial wall motion, volumes and LV ejection fraction obtained using Myoview GSPECT with those from cine MRI in patients with acute myocardial infarction to see if evaluation of LV function in the presence of hypoperfused segments can be done accurately.

Subjects and Methods: This study prospectively evaluated 25 patients with acute MI referred for evaluation of myocardial perfusion. All patients underwent gated Myoview SPECT at rest with 25-30 mCi of Myoview. Resting cine MRI of the heart with ECG triggering was done in all subjects within 48 hours to serve as a comparator for the resting GSPECT LV function assessments. Gated SPECT and MRI were performed 5 ± 2days and 6 ± 2days, respectively, after the onset of acute MI.

Data Processing: SPECT images were acquired using a 90-degree dual-headed system, obtaining a 180-degree arc with 64 stops (32 per head) of 30 seconds each. Reconstructed trans-axial images were re-formatted into short, vertical long and horizontal long axes at 8 frames per cardiac cycle; LV volumes and LVEF were computed for the GSPECT images using operator-independent commercial software. For the cine MRI, a 1.5 tesla unit was used. Using Simpson's rule, LVEF and volumes were computed from the horizontal long and short axis MRI slices, selected by a trained radiologist blinded to the GSPECT results. For both modalities, wall motion was reported as a score for each of 13 ventricular segments (a 5-point scale from 3 = normal to –1 = dyskinetic).

Statistical Methods: For LVEF and volumes, the Student's T-test was used as well as descriptive statistics. For wall motion scores, the modalities were compared using Cohen's kappa statistics. The agreement of the summed wall motion scores was measured by Pearson's correlation coefficients and reported on conventional and Bland-Altman plots. Inter- and intra-observer agreement were not evaluated.

Summary of Results and Findings: A total of 325 LV myocardial segments were evaluated. For wall motion, agreement in scores was excellent for individual segments and summed scores, as indicated in table #4.d.3 below. Agreement segments are highlighted:

Table #4.d.3: Agreement between gated SPECT and cine MRI for assessment of regional wall motion

Gated SPECT	Cine MRI			
	Normal	Mild hypokinesis	Severe hypokinesis	Akinesis/dyskinesis
Normal	233	0	0	0
Mild hypokinesis	13	27	0	0
Severe hypokinesis	3	2	26	5
Akinesis/dyskinesis	0	0	2	14

Ref. vol. 26, p. 129 of submission

Kappa for agreement of individual segment scores was 0.82. For the summed scores, r was 0.94 and p was < 0.0001. The Bland-Altman plot showed no trends when the absolute difference between summed scores was compared to the mean wall motion score as computed using MRI and GSPECT. For LVEF, end-systolic volume and end-diastolic volumes, r-values were 0.93, 0.9 and 0.81, respectively, and p was < 0.0001 for all 3 parameters. For LVEF, MRI values tended to exceed GSPECT values by approx. 10%, a deviation likely caused by the use of 8-frame gating for the SPECT images. In addition, since MRI was performed up to 48 hours after GSPECT in these acute patients, recovery from post-MI stunning of myocardium before MRI may explain the higher LVEF.

Conclusions: Again the results show an excellent overall correlation of wall motion scores and LVEF/volumes between GSPECT and gated MRI. Unlike in Reference #10, poor uptake in hypoperfused segments of myocardium did not appreciably reduce the agreement scores and kappa values for wall motion in these segments. The explanation provided for differences in LVEF between the two modalities is the same as that provided in the pivotal studies in the NDA.

Article # 17: Wahba et. al. Feb. 2001. *Nuclear Medicine Communications*, vol. 22, pp. 175-182

Title: "Detection of residual wall motion after sustained myocardial infarction by gated ^{99m}Tc tetrofosmin SPECT: a comparison with echocardiography"

Purpose of study: To analyze the concordance of myocardial wall motion scores obtained using Myoview GSPECT with those from 2-dimensional echocardiography in patients with previous myocardial infarction, and to analyze the agreement between wall motion scores and myocardial perfusion.

Subjects and Methods: This study prospectively evaluated 25 patients with previous MI referred for evaluation of myocardial perfusion. All patients underwent gated Myoview SPECT at rest and during pharmacologic or exercise stress (18 for a 2-day protocol at 13.5 mCi/day and 7 for a 1-day protocol with 6.8 mCi at rest and 20.3 mCi at stress). Echocardiography without contrast was done in all subjects within 2 weeks of GSPECT to serve as a comparator.

Data Processing: SPECT images were acquired using a triple-headed system, obtaining a 360-degree arc with 90 4-degree stops of 35 seconds each. Reconstructed trans-axial images were re-formatted into short, vertical long and horizontal long axes at 16 frames per cardiac cycle; LV volumes and LVEF were computed for the GSPECT images, but were not compared to the echocardiograms. Wall motion was evaluated by readers blinded to echo results from a 3-dimensional image reconstructed from the GSPECT data using commercially available software.

For echocardiography, parasternal long-axis, short-axis and apical 4- and 2-chamber views were obtained and selected by a trained radiologist blinded to the GSPECT results. For GSPECT, wall motion was reported as a score for each of 20 ventricular segments, while for echo, the heart was divided into 16 segments. For the purpose of matching GSPECT with echo, the segments were regrouped into a 7-region model. Motion in each region was rated on a 4-point scale from 1 = normal to 4 = dyskinetic. Each of the segments was also rated for perfusion by reporting Myoview uptake on a 4-point scale: 0 = absent to 3 = normal.

Statistical Methods: For regional wall motion scores, the modalities were compared using Cohen's kappa statistics. The prevalence of abnormal wall motion according to the 2 modalities were compared using McNemar's test. Inter- and intra-observer agreement were not evaluated.

Summary of Results and Findings: A total of 175 LV myocardial segments were evaluated. Agreement in individual scores was 80% overall, 84% for regions with normal or minimally reduced perfusion, and 70% for regions with severely reduced or absent perfusion. Table #4.d.4 below summarizes the regional score agreements (highlighted):

Table #4.d.4: Score agreement between echo and gated SPECT for assessment of regional wall motion

Echocardiography	Gated SPECT			
	Regions with normal or slightly reduced perfusion (N = 119)		Regions with severely reduced or no perfusion (N = 56)	
	Normal or hypokinetic	Akinetic or dyskinetic	Normal or hypokinetic	Akinetic or dyskinetic
Normal or hypokinetic	97	6	19	10
Akinetic or dyskinetic	12	0	7	20

Ref. derived from Tables 2 and 3, vol. 26, p. 140 of submission

Conclusions: Overall, the results show a high degree of correlation of wall motion scores between GSPECT and gated MRI. For regions of good perfusion (> 55% normal tracer uptake), the agreement was better than for areas of severe hypoperfusion or absent perfusion. As in Reference #10, poor uptake in hypoperfused segments of myocardium

have reduced the agreement scores for wall motion in these segments The explanation the authors provided for differences in wall motion scores between the two modalities was that the low count rate was inadequate to properly visualize the hypoperfused regions.

Article # 18: Wahba et. al. Apr. 2001. *Eur. J. of Nuclear Medicine,* vol. 28, pp. 514-521

Title: "Detection of residual wall motion after myocardial infarction by gated ^{99m}Tc tetrofosmin SPET: a comparison with contrast ventriculography"

Purpose of study: To analyze the concordance of myocardial wall motion scores obtained using Myoview GSPECT with those from contrast left ventriculograms in patients with previous myocardial infarction, and to analyze the agreement between wall motion scores and myocardial perfusion. It appears that this paper is based on the same group of post-MI patients that were studied in Reference #17, with one additional subject.

Subjects and Methods: This study prospectively evaluated 26 patients with previous MI referred for evaluation of myocardial perfusion. All patients underwent gated Myoview SPECT at rest and during pharmacologic (adenosine) or exercise stress using the same Myoview doses as in Ref. #17. Contrast left ventriculography (LVG) was done in all subjects within 2 weeks of GSPECT to serve as a comparator. The LAO and RAO LVG views were divided into a total of 7 regions to be compared to the GSPECT images.

Data Processing: SPECT images were acquired using a Toshiba 3-headed camera, obtaining a 360-degree acquisition using the same protocol as in Ref. #17. Reconstructed trans-axial images were re-formatted into short, vertical long and horizontal long axes at 16 frames per cardiac cycle; LV volumes and LVEF were computed for the GSPECT images, but were not compared to the ventriculograms. Wall motion was evaluated by readers blinded to angio results from a 3-dimensional image reconstructed from the GSPECT data using commercially available software. Motion in each of 7 regions was rated on a 4-point scale from 1 = normal to 4 = dyskinetic. Perfusion to each region was also rated by reporting uptake in non-gated images from 0 = absent to 3 = normal.

For contrast ventriculography, LAO and RAO views were obtained and evaluated by a trained cardiologist blinded to the GSPECT results. For the purpose of matching GSPECT with the angiograms, the long-axis and 3 short-axis slices of the gated SPECT were manually aligned with the corresponding segments on the left ventriculogram.

Statistical Methods: For regional wall motion scores, the modalities were compared using Cohen's kappa statistics. The prevalence of abnormal wall motion according to the 2 modalities were compared using McNemar's test. The summed wall motion scores were compared by linear regression and Pearson's correlation coefficients. Again, inter- and intra-observer agreement were not evaluated.

Summary of Results and Findings:

A total of 182 myocardial segments were evaluated. Agreement in individual scores was 80% overall (κ = 0.67, p <0.001), 82% for regions with normal or minimally reduced perfusion (κ = 0.69, p <0.001), and 67% for regions with severely reduced or absent perfusion (κ = 0.56, p <0.001). Table #4.d.5 below presents the scores given to the myocardial regions by each modality. Agreement segments are highlighted:

Table #4.d.5: Score agreement between LVG and gated SPECT for assessment of regional wall motion

Contrast ventriculography	A) Gated SPECT				
	Normal	Hypokinetic	Akinetic	Dyskinetic	Total
Normal	73	17	1	2	93
Hypokinetic	4	56	4	0	64
Akinetic	1	4	12	0	17
Dyskinetic	0	3	1	4	8
Total	78	80	18	6	182

Ref. Table 31, p. 146, vol. 26 of submission

Conclusions: Overall, the results show a very similar pattern of correlation to that presented in Reference #17, with overall 80% agreement in regional wall motion scores, and better agreement in well-perfused regions than poorly perfused ones. The results are not surprising, as they are probably obtained from the same patients as in Ref. #17.

4. Reviewer's Conclusions and Overall Observations from the Literature

It is clear from Tables #4.d.1 and 4.d.2 above that, although none of the 22 articles met all of the criteria listed in the Guidance to be used in support of the GSPECT LV function indication, several had more than 5 of the attributes listed, and overall, with 1 exception (article #20 by Wright et. al) the papers came to the conclusion that LV function (ejection fraction and regional wall motion) could be reliably evaluated using Myoview GSPECT; the results closely reflected those obtained with LV angiography, radionuclide ventriculography, ultrasound or gated MRI. Despite its negative conclusion (due to broad confidence intervals for GSPECT LVEF values), Article #20 had r-values of 0.81 and 0.82 for 8- and 16-frame gated SPECT when LVEF values were compared to radionuclide ventriculography. Nearly all of the submitted articles had a prospective study design and 9 of the studies utilized blinded readers. All had a statistical plan and clearly defined endpoints.

The most significant weakness of GSPECT imaging indicated in the literature articles was the difficulty assessing regional wall motion in hypoperfused segments, which is not unexpected. Clearly one needs to visualize a segment to make a reliable assessment of its motion. On the other hand, if a myocardial perfusion agent fails to show reduced uptake in areas of ischemia or infarction, it fails to perform for that indication. To compute LV ejection fraction and volumes, however, it is not as critical as with wall motion to clearly visualize all regions of the myocardium, and this is substantiated by the excellent overall agreement results for LVEF by GSPECT and the comparator modalities seen in the literature submitted with this application. As suggested by the applicant in the Integrated Summary of Efficacy, the performance of GSPECT in calculating LVEF appears to be more dependent on the software (and hardware) used for imaging than the particular perfusion agent chosen for the study. However, generation of a region-of-interest is still based on operator visual interpretation, and areas of ischemia (reduced uptake) may limit the effectiveness of edge-detection software.

D.4.e. Efficacy Summary and Conclusions, Issues of Concern and Recommendations

In NDA #20,372 SEI-013, the applicant is seeking a new indication for Myoview: the assessment of ventricular function in patients being evaluated for heart disease and/or ventricular function.

In two pivotal Phase 3 studies, the applicant has demonstrated that Myoview GSPECT has acceptable sensitivity and specificity as well as accuracy for detecting abnormalities in global LV function (as defined by an ejection fraction of <50% or the presence of a wall motion abnormality on the truth standard MUGA exam). The correlation of LV ejection fraction numerical values between the two modalities was also good for all blinded readers (Spearman's correlation coefficients for the individual readers ranging from 0.70 to 0.81 in the two studies). Table #4.e.1 below summarizes sensitivity, specificity and accuracy for subject-level LVEF; Table #4.e.2 summarizes the same for subject-level wall motion. For both parameters, results are pooled across the 3 blinded readers for each study. For each table, N = the number of diagnostic LVEF or wall motion readings based on both GSPECT and MUGA imaging; LCB = lower bound of the 95% confidence interval.

Table #4.e.1: Sensitivity, Specificity, Accuracy of Myoview GSPECT for LVEF

Pool	Sensitivity		Specificity		Accuracy	
	N	%, 95% LCB	N	%, 95% LCB	N	%, 95% LCB
All readers: Study MYO-301	168	87.5 (80.3)	207	77.3 (68.9)	375	81.9 (76.2)
All readers: Study MYO-303	205	81.0 (73.2)	301	84.4 (78.4)	506	83.0 (78.3)
All readers: both studies	373	83.9 (78.6)	508	81.5 (76.6)	881	82.5 (78.9)

Ref. Table #9.2.1.1.2, p. 52, vol. 27 (ISE) (subject-level, pooled across readers)

Table #4.e.2: Sensitivity, Specificity, Accuracy of Myoview GSPECT for Wall Motion

Pool	Sensitivity		Specificity		Accuracy	
	N	%, 95% LCB	N	%, 95% LCB	N	%, 95% LCB
All readers: Study MYO-301	181	86.2 (80.2)	186	74.7 (68.1)	367	80.4 (75.8)
All readers: Study MYO-303	184	84.8 (78.1)	313	80.2 (74.6)	497	81.9 (77.6)
All readers: both studies	365	85.5 (81.0)	499	78.2 (73.9)	864	81.3 (78.1)

Ref. Table #9.2.2.1.2, p. 58, vol. 27 (ISE) (subject-level, pooled across readers)

Subgroup analyses were conducted of the combined LVEF efficacy results from the two studies, by age group (below 65 and 65 or older), gender, cardiac medical history, LV chamber size and 1- vs. 2-day imaging protocol. Review of these analyses showed a tendency for higher sensitivity in patients 65 and older, males, patients with large hearts, those undergoing 2-day imaging and those with a history of MI. Specificity was higher in the older age group, women, patients with only suspected CAD, those with small or normal LV chamber size and those undergoing 1-day imaging. Concerns raised during review of the efficacy database, discussed in the reviews of Studies MYO-301 and 303 (Section D.4.c), are highlighted below:

Efficacy issues of concern

- Use of accuracy as a primary endpoint

  As endpoints for diagnostic efficacy, sensitivity and specificity are preferred over accuracy by the Division of Medical Imaging at FDA because they are not dependent on disease prevalence. Though sensitivity and specificity for abnormal LVEF and wall motion were considered by the applicant as secondary and not primary endpoints, they were reviewed as though they were primary for their potential supportive value.

- Comparison of a stress GSPECT study with a resting MUGA exam

  In Studies MYO-301 and 303, GSPECT images acquired after treadmill exercise were compared to MUGA images obtained at rest one to five days later. Although the GSPECT acquisition was begun 15 to 45 minutes after exercise was completed, the potential still exists for residual ischemia ("stunning") to be present at the time of acquisition. This would increase the likelihood of a stress-induced wall motion or LVEF abnormality to appear on GSPECT but not the subsequent resting MUGA examination (see next page).

- Underestimation of LVEF by gated SPECT in patients with poor LV function

  The tendency for GSPECT to underestimate LVEF at low values in the pivotal trials is explained well: "truncation" of the time-activity curve for GSPECT by 8-frame gating, and the possibility of post-stress "stunning" reducing myocardial contraction during the stress GSPECT acquisition. This may be a direct consequence of comparing a stress GSPECT study with a resting MUGA exam (see above). However, the applicant has not adequately analyzed LVEF values in the subgroup of patients who had evidence of ischemia during stress (angina, ST-depression, myocardial perfusion defect on Myoview) to further substantiate the theory of a stress-induced wall motion abnormality as an explanation for lower stress GSPECT LVEF values. A subgroup analysis of efficacy in those patients experiencing myocardial ischemia during exercise would be helpful to address this issue. Comparing the *resting* GSPECT scans with the MUGA study would also exclude stress-induced ischemia as a contributing factor to the differences in *resting* LVEF values. Resting GSPECT data was not submitted in the application, however, it was performed as part of the study. Another possible cause for underestimation of LVEF may be poor ROI selection caused by poor myocardial visualization in ischemic areas.

- Overestimation of LVEF in patients with small hearts

  For patients with normal to high LVEF (especially women with small LV chamber size) the potential for GSPECT to underestimate end-systolic volume (and overestimate LVEF) exists. The dataset in this supplement has shown that most outliers whose LVEF by GSPECT exceeded the LVEF by MUGA by 20% or more were females with small hearts and ejection fractions $\geq$ 72%. This overestimation has been reported in the literature (References #35: Evereart et. al. and #36: Ford et. al., vol. 29, pp. 225-244), and is most likely due to the limited resolution of the system where each voxel (volume element) represents a considerable portion of the LV volume, especially at end-systole. In the opinion of this reviewer, this provides a reasonable explanation. In any case, this problem is most likely related to limitations of the hardware and software used for imaging and not the radiopharmaceutical itself.

- Concerns raised during review of the literature

  The most significant weakness across the literature database was the difficulty assessing regional wall motion in hypoperfused myocardial segments. To make a reliable assessment of its motion on a cine SPECT study, one needs to visualize the myocardium. On the other hand, if a myocardial perfusion agent fails to show reduced uptake in areas of ischemia or infarction, it fails to perform as a perfusion agent. To compute LV ejection fraction and volumes, however, it is not as critical to clearly visualize all regions of the LV myocardium, and this is substantiated by the excellent overall agreement results for LVEF by GSPECT and the comparator modalities seen in the literature submitted with this application.

Efficacy conclusions

Despite the issues of concern indicated above, it is apparent that the data submitted for the two pivotal studies and the submitted literature is adequate to support an indication of evaluating LV function using Myoview GSPECT. As suggested by the applicant in the Integrated Summary of Efficacy, the performance of GSPECT in calculating LVEF appears to be more dependent on the software (and hardware) used for imaging than the particular perfusion agent chosen for the study.

Recommended action for efficacy: APPROVAL

Recommendations to address the efficacy concerns:

- Subgroup analysis of efficacy in patients with ischemia during exercise stress (Phase 4 commitment, not necessary before approval)
- Changes in the labeling as indicated in Section #D.8.c.

D.4.f. Input from Statistics: Efficacy

The Statistical Review by A. Mucci, Ph.D. was not available at the time of writing this review.

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D. 5. Integrated Review of Safety

D.5.a. Introduction and Safety Database for SEI 013

The safety database for this efficacy supplement comprises the results of safety assessments in the two pivotal studies MYO-301 and 303. These are submitted in the reports for each of the two studies and pooled in the Integrated Summary of Safety (vol. 30). In addition, a brief overview of the safety results of MYO-302, a study investigating myocardial perfusion imaging in subjects undergoing pharmacologic stress with adenosine or dipyridamole was submitted. The safety results of three European studies of Myoview as a breast cancer imaging agent (P53-020, 022 and 024) are also summarized, as well as post-marketing experience from 9 Feb. 1996 to 1 March 2002. A 4-Month Safety Update was submitted on 23 August 2002; a review of this may be found in Appendix 2.

- Adequacy of the Safety Database: Review of the safety results for the two clinical trials has uncovered no serious deficiencies and flaws which would render the clinical database unable to assure the safety of Myoview in the setting of GSPECT imaging in cardiac patients. Safety testing in these studies included adverse event monitoring to completion of the MUGA exam (1 to 5 days after the 2nd Myoview injection), vital signs, ECG's and a limited cardiopulmonary physical examination.

- Radiation and Dosimetry: In Studies MYO-301 and 303, the doses used for rest ranged from 7.3 to 13.4 mCi for the 1-day protocol and 13.8 to 26.8 mCi for the 2-day protocol. This range is in excess of the approved 5 to 8 mCi range approved for this injection (See Section #D.6: Dosing and Administration Issues) and D.8.c: Labeling Review). The doses for exercise stress imaging are according to the approved labeling and range from 14.5 to 27.0 mCi. The whole-body dose from Myoview is reported in the label as being 0.032 rad/mCi (8.61×10^{-3} mSv/mBq). The critical organ is the gallbladder wall, for which absorbed dose is 0.123 rad/mCi. The dose to the whole body, liver and other organs from a total of 45 mCi (maximum for 1 day protocol according to the proposed package insert), including testes (0.58 rad) and ovaries (1.30 rad) are acceptable to this reviewer. The maximum total dose for rest and stress imaging (2-day protocol) in the label is 66 mCi (33 x 2). For details on dosimetry, please refer to the Biopharmaceutics review for the original Myoview NDA.

D.5.b. Demographics and Extent of Exposure

1. Demographics of the Safety Database

Demographics for the patients enrolled in the two trials are given in Table #5.b.1 below. As indicated in the table, 65.5% of the patients were male; the mean age overall was 60.5 years, range 20 to 88 years. No healthy volunteers were recruited in either study. A total of 336 patients were enrolled, 329 of whom received at least 1 dose of Myoview in the two clinical trials.

TABLE #5.b.1: Demographic Characteristics (All patients enrolled in both studies)

Demographic Parameter		MYO-301 (145)	MYO-303 (191)	Overall (336)
Sex:	Male	102 (70.3%)	118 (61.8%)	220 (65.5%)
	Female	43 (29.7%)	73 (38.2%)	116 (34.5%)
Race:	White	117 (80.7%)	162 (84.8%)	279 (83.0%)
	Black	21 (14.5%)	26 (13.6%)	47 (14.0%)
	Asian	1 (0.7%)	0	1 (0.3%)
	Other	6 (4.1%)	3 (1.6%)	9 (2.7%)
Age (years)	Mean ± SD	61.2 ± 11.7	59.9 ± 12.7	60.5 ± 12.3
	Range	30-88	20-88	20-88
Weight (kg)	Mean ± SD	85.0 ± 19.4	86.6 ± 19.8	85.9 ± 19.6
	Range	52-150	47-163	47-163
Height (cm)	Mean ± SD	170.7 ± 9.9	171.0 ± 10.1	170.9 ± 10.0
	Range	137-191	147-193	137-193
BMI (kg/m^2)	Mean ± SD	29.2 ± 6.1	29.6 ± 5.9	29.4 ± 6.0
	Range			

Ref. derived from Table #8.1.1, p. 38, vol. 30.

Among the 336 patients enrolled, 227 had a specific cardiac history (67.6%), 125 had angina (37.2%), 121 had a prior myocardial infarct (36.0%), 110 had a coronary angioplasty (32.7%), 73 had bypass surgery (21.7%) and 100 had congestive heart failure (29.8%). A smoking history (current or past) was reported in 230 patients (68.5%). For MYO-301, the percentage of specific cardiac histories was greater (77.9%) than for MYO-303 (59.7%); and the proportion of males was higher (70.3% versus 61.8%). For MI, angina, CHF and CABG, the percentages were also correspondingly higher for MYO-301. This may have been a contributing factor in the difference in AE incidence between the studies.

2. Dosing and Extent of Exposure

The proposed dose for labeling and marketing is 5-12 mCi for the rest dose and 15-33 mCi for the stress dose in a 1-day protocol, and 5-33 mCi for each dose in a 2-day protocol. In the two studies, the common protocol called for 9-12 mCi of Myoview to be given at rest for the 1-day protocol; 15-24 mCi of Myoview was to be given at rest for the 2-day protocol. For stress, 15-24 mCi was to be given in both protocols. The breakdown of actual exposure is given below:

- 1 dose of Myoview given to 4 patients.
- Low rest of Myoview given to 290 patients in both studies.
- High rest dose of Myoview given to 39 patients in Studies MYO-301 and 303.
- Stress dose of Myoview given to 325 patients in Studies MYO-301 and 303.
- Mean low rest dose per injection 10.3 ± 1.4 mCi, range —— mCi (both studies).
- Mean high rest dose per injection: 18.1 ± 3.9 mCi , range , —— mCi (both studies).
- Mean stress dose per injection: 22.9 ± 1.6 mCi, range —— mCi (both studies)

The majority of patients given the high rest dose (2-day protocol) were in Study MYO-303 (36 of 39 patients). Of the 336 patients enrolled in the two studies, 311 (92.6%) were given a 15 to 20 mCi dose of —— labeled red cells for the MUGA exam, and 310 patients (92.3%) underwent MUGA imaging. The actual doses of —— for each patient were not reported.

D.5.c. Specific Findings of the Safety Review

1. Adverse Events

a. Overview and Table of Adverse Events

An adverse event (AE) was defined by the sponsor as a symptom reported on the CRF. WHO-ART criteria were used to categorize the events. As indicated in the reviews of Studies MYO-301 and 303, patients underwent rest Myoview dosing, followed by exercise stress and subsequent stress Myoview dosing. A substantial number of the patients experienced symptoms which the investigator attributed to exercise stress. These include but are not limited to pain, tightness or pressure in the chest, arms, head or upper body, dizziness, lightheadedness, leg fatigue/cramps, dyspnea, flushing and anxiety. All AE's were reported, whether or not the investigator judged them to be due to exercise stress or Myoview.

None of the 47 adverse events reported were attributed by the investigator to Myoview. Four adverse events took place before stress (headache, nausea, pneumonia and anxiety). Table #5.c.1 below indicates the frequency of AE's of each type in the two studies.

TABLE #5.c.1: Adverse Events in 47 Subjects in NDA #20,372 SEI 013 by Body System: N, (%)

ADVERSE EVENT WHO Body System	MYO-301 (N = 142)		MYO-303 (N = 187)		Combined (N = 329)	
	# Subjects, %	# Events	# Subjects, %	# Events	# Subjects, %	# Events
Total	31 (21.8)	40	7 (3.7)	7	38 (11.6)	47
Body as a Whole						
Chest pain	4 (2.8)	4	2 (1.1)	2	6 (1.8)	6
Fatigue	3 (2.1)	3	0	0	3 (0.9)	3
Local edema at injection site	1 (0.7)	1	0	0	1 (0.3)	1
Syncope	2 (1.4)	2	0	0	2 (0.6)	2
Cardiovascular						
Angina pectoris	1 (0.7)	1	0	0	1 (0.3)	1
Extrasystoles	1 (0.7)	1	0	0	1 (0.3)	1
Cardiomegaly	1 (0.7)	1	0	0	1 (0.3)	1
ECG changes	6 (4.2)	6	0	0	6 (1.8)	6
Hypertension	1 (0.7)	1	0	0	1 (0.3)	1
Hypotension	1 (0.7)	1	0	0	1 (0.3)	1
Peripheral Vascular						
Phlebitis at injection site	1 (0.7)	1	0	0	1 (0.3)	1
Pulmonary						
Bronchospasm	1 (0.7)	1	0	0	1 (0.3)	1
Dyspnea	1 (0.7)	1	0	0	1 (0.3)	1
Pneumonia	1 (0.7)	1	0	0	1 (0.3)	1
Pulmonary congestion	1 (0.7)	1	0	0	1 (0.3)	1
Gastrointestinal						
Diarrhea	0	0	1 (0.5)	1	1 (0.3)	1
Dry mouth	1 (0.7)	1	0	0	1 (0.3)	1
Nausea	3 (2.1)	3	2 (1.1)	2	5 (1.5)	5
Musculo-skeletal						
Arthralgia	1 (0.7)	1	0	0	1 (0.3)	1
Skeletal pain	1 (0.7)	1	0	0	1 (0.3)	1
Metabolic and Nutritional						
Hypoglycemia	1 (0.7)	1	0	0	1 (0.3)	1
Psychiatric						
Insomnia	1 (0.7)	1	1 (0.5)	1	2 (0.6)	2
Nervousness	0	0	1 (0.5)	1	1 (0.3)	1
CNS, Peripheral Nerves, Eyes						
Dizziness	2 (1.4)	2	0	0	2 (0.6)	2
Headache	2 (1.4)	2	0	0	2 (0.6)	2
Cataract	1 (0.7)	1	0	0	1 (0.3)	1
Other						
Fall	1 (0.7)	1	0	0	1 (0.3)	1

(Ref. derived from Table #10.3.1, p. 49, vol. 30 (ISS)

In the two pivotal studies, the most common AE's were chest pain (6 patients or 1.8%), ST-T wave ECG changes (6 or 1.8%) and nausea (5 or 1.5%). Two of the subjects receiving Myoview in the two trials experienced a serious adverse event (hypoglycemia and syncope). One patient withdrew after developing syncope associated with a vaso-vagal reaction following venipuncture. Of the 47 adverse events in this dataset, none were considered by the sponsor and this reviewer to have a relationship to Myoview. There were no anaphylactic or anaphylactoid reactions. Two injection site reactions (edema and mild phlebitis) were reported, but the second Myoview dose was not withheld for safety reasons in either case.

Noteworthy is the difference in AE incidence (chest pain and ECG changes) between the two studies (21.8% for MYO-301 and 3.7% for MYO-303). The sponsor was not able to explain the difference, but the higher incidence of cardiac disease in MYO-301 (77.9% as opposed to 59.7%) may partially explain the higher incidence of these events seen in that study. Other explanations included possible differences in reporting practices among observers and random variability, all which appear reasonable to this reviewer.

b. Subgroup Analyses of Adverse Events (both trials combined)

As indicated above, four AE's took place prior to exercise stress. The episode of "pneumonia" actually represented scattered rhonchi, reclassified as pneumonia as a WHO-ART preferred term. These were noted before Myoview dosing as well as at all subsequent visits. Division of patient groups into low vs. high Myoview dose (for 1- or 2-day rest/stress protocols), concurrent medications, age (<65 vs. ≥65 years), gender, weight and NYHA grade did not reveal any trends or effects of any demographic characteristic on the AE rate.

c. General Comments and Conclusions: Adverse Events

Given the low incidence of AE's prior to exercise (four: headache, nausea, nervousness, pneumonia), lack of trends among subgroups, similarity to the AE profile in the original NDA and patient population being studied, it appears that the AE profile presented in this supplement is what one may expect to see in cardiac patients undergoing exercise stress. No data reviewed suggested a causal role to this reviewer for Myoview in these events.

2. Deaths, Withdrawals and Serious Adverse Events

There were no deaths in the MYO-301 or 303 study reports. One withdrawal took place after rest dosing due to anxiety and subsequent syncope after venipuncture (Subject #013-0031 in MYO-301). Two SAE's (syncope and a hypoglycemic episode) took place in Study MYO-301; brief narratives are presented below. Review of the CRF's indicate no findings to implicate a possible causal role of Myoview.

a. SYNCOPE: Subject #016-0007 is a 44 year old white male with hypertension, hyperlipidemia, angina and 2 prior PTCA's , taking Plavix, Altace, Lipitor, atenolol and aspirin. The rest and exercise Myoview doses (8.7 and 24.3 mCi) were given without incident, except for intermittent AV block on the ECG during stress. Five days later, ——) red cells were given for the MUGA study. Four minutes after —— dosing, the patient felt hot, then fainted. Asystole, unresponsiveness and apnea lasted approx. 30 seconds. After oxygen was administered, the patient recovered completely and the MUGA images were acquired and no further treatment was given. The investigator attributed this SAE to a vasovagal reaction and not Myoview or the —— labelled red cells.

b. HYPOGLYCEMIC REACTION: Subject #016-0026 is a 41-year old white male with CAD and insulin-dependent diabetes mellitus with neuropathy, hypertension, hyperlipidemia, angina, ischemic cardiomyopathy and depression. Concomitant medications included atenolol, Lipitor, paoxitene, Xanax, insulin, Lasix, nitropatch, nitroglycerin and aspirin. ECG changes during exercise stress included ST-T wave changes and PVC's. Two days after the rest/stress Myoview study (8.8 and 23.4 mCi), the patient was found unresponsive at home, and transported by ambulance to the ER. IV fluids given included dextrose; the patient awakened and was discharged. Blood glucose levels were not reported. the investigator attributed this SAE to diabetes and insulin therapy.

3. Vital Signs (Systolic, diastolic BP, pulse, respirations, temperature)

Systolic and diastolic blood pressure, pulse, temperature and respirations were taken in both studies, however, vital sign results for the combined studies are discussed in this section. Table #5.c.2 presents normal ranges and criteria for significant changes at rest, established prospectively and consistent throughout both clinical trials. For treadmill exercise, the cutoff level for blood pressure was 225 mm Hg systolic and 110 mm Hg diastolic at maximal workload. For heart rate, the reference limit was 220 minus the subject's age. With the exception of diastolic pressure, whose "significant change" should be 10 mm Hg, the criteria for significant changes and cut points are appropriate to this reviewer.

TABLE #5.c.2: Vital Signs: Normal Ranges at Rest (ref. p. 24, vol. 5)

Parameter	Normal range	Significant change criteria
Heart Rate	60-100 bpm	>10 beats/min
Systolic Blood Pressure	85-139 mm Hg	>20 mm Hg
Diastolic Blood Pressure	60-89 mm Hg	>20 mm Hg
Respirations	12-22 breaths/min.	>10 breaths/min.
Temperature (oral)	97.5- 99.9 ° C.	>1.5 ° C.

a. Capture and Reporting of Vital Sign Data

Blood pressure and pulse were captured at 10 min. before and after rest Myoview dosing, 10 min. before starting exercise stress, at 2- minute intervals during stress, and 5-minute intervals during recovery until BP and pulse returned to within 5% of baseline values. Body temperature and respirations were measured at 10 min. pre-rest dose, 10 min. after rest dose and 10 min. before exercise began. For each parameter, the mean pre- and post-dose values were computed. With respect to systolic and diastolic blood pressure, the more clinically meaningful "paired" values were not analyzed, only isolated systolic and diastolic readings.

b. Findings in the Reported Vital Signs Data

Table #5.c.3 below indicates the total N, mean, SD, minimum and maximum values, and changes from baseline in resting exam vital signs for both studies:

TABLE #5.c.3: Vital Signs: Mean and Limits of Values and Changes from Baseline (ref. p. 60,61, vol. 30, ISS)

Parameter	Time Point	N	Mean (SD) [min., max]	Change from Baseline[a]			
				Decrease		Increase	
				n	%	n	%
Heart Rate (bpm)	Baseline	329	67.6 (12.8) [40, 108]				
	10 Minutes	329	66.7 (12.1) [40, 108]	20	6.1	10	3.0
Systolic Blood Pressure (mm Hg)	Baseline	329	131.5 (18.8) [80, 196]				
	10 Minutes	329	129.6 (17.6) [80, 196]	8	2.4	2	0.6
Diastolic Blood Pressure (mm Hg)	Baseline	329	77.9 (9.6) [46, 104]				
	10 Minutes	329	77.3 (9.4) [46, 104]	2 (8 >10mm)	0.6 (2.4 >10mm)	0 (5 >10mm)	0 (1.5 >10mm)
Respirations (rpm)	Baseline	329	16.8 (2.7) [10, 30]				
	10 Minutes	329	16.8 (2.8) [10, 30]	0	0	0	0
Temperature (oral) °C	Baseline	329	36.6 (0.5) [35, 38]				
	10 Minutes	329	36.6 (0.4) [35, 38]	0	0	1	0.3

[a] Significant changes defined in Table #5.c.2 above. For diastolic BP, # of changes > 10mm are also reported.

c. General Comments and Conclusions: Vital Signs:

The above table and data listings for resting vital signs show no significant trends. Changes in blood pressure and pulse during exercise were as expected in a cardiac population subjected to treadmill stress. No trends were noted in shift tables or scatterplots for BP, pulse, respirations or temperature to implicate any role of Myoview in these changes.

4. Electrocardiograms

a. Capture and Reporting of ECG Data

Electrocardiograms (12-lead) were obtained in all subjects given Myoview. In both studies, the test was obtained at the same time as pulse and blood pressure: 10 min. before and after rest Myoview dosing, 10 min. before starting exercise stress, at 2- minute intervals during stress, and 5-minute intervals during recovery until BP and pulse returned to within 5% of baseline values. Table #5.c.4 below presents normal ranges and criteria for significant ECG changes at rest, established prospectively and consistent throughout both clinical trials. Continuous ECG monitoring was done during exercise stress in all patients. The significant change criteria and cut points are appropriate to this reviewer.

TABLE #5.c.4: Electrocardiograms: Normal Ranges (ref. p. 24, vol. 5)

Parameter	Normal range at rest	Significant change criteria
PR Interval	120-200 msec	≤4 msec, 5-24 msec, >24 msec
RR Interval	600-1000 msec	Any deviation from normal range
QRS Interval	50-100 msec	Any deviation from normal range
QTc Interval (Bazzett's formula)	<440 msec at rest <460 msec during exercise stress	≤30 msec, 31-60 msec, >60 msec

Post-dose electrocardiographic changes which raise a major safety concern are premature ventricular contractions (PVC's) and the prolongation of the QTc interval, which can be a harbinger of the life-threatening arrhythmia *torsades-de-pointes*. No cases of *torsades* were reported in the MYO-301 or 303 clinical database.

Six of the changes reported in the subject ECG data listings or discussion of ECG's were considered to be adverse events. All of the patients were in Study MYO-301, and all had ST-T wave changes during exercise stress. None of these AE's were associated with PR, QRS, QTc prolongation or other ECG changes. One patient was reported to have "bi-atrial enlargement" which was not associated with any symptoms. The decision to call an ECG change an AE was at the discretion of the investigator; no pre-set criteria were applied.

b. Findings in the Reported ECG Data

Table #5.c.5 on the next page indicates the total N, mean, SD, minimum and maximum values, and changes from baseline in resting PR and QTc's for both studies. The mean changes from baseline are not significant, however, 90 patients' QTc were outside the reference range at baseline and 94 after rest Myoview dosing. Review of data listings for these patients and the study reports for both studies was conducted, and no differences were seen between low (1-day) and high (2-day) dose groups with respect to rest and exercise changes in the ECG parameters.

TABLE #5.c.5: 12-Lead ECG: Mean, Limits of PR and QTc and Changes from Baseline

Parameter	Time Point	N	Mean (SD) Interval Values [min., max]	Above Reference Range n (%)	Mean (SD) Change from Baseline [min., max]	Change from Baseline (msec)			
						Decrease >24 PR ≥61 QTc	Decrease 5-24 PR 31-60 QTc	Increase 5-24 PR 31-60 QTc	Increase >24 PR ≥60 QTc
PR Interval (msec)	Baseline	323	167.1 (31.7) [35, 320]	30 (9.3%)		n (%)			
	10 Minutes	322	168.7 (32.9) [31, 320]	31 (9.7%)	1.3(15.6)	11 (3.4%)	42 (13.1%)	57 (17.8%)	15 (4.7%)
QTc Interval (msec)	Baseline	318	425.6 (54.9) [240, 1022]	90 (28.3%)		n (%)			
	10 Minutes	315	423.8 (54.7) [251, 1039]	94 (30.4%)	-2.1 (31.0)	9 (2.9%)	20 (6.5%)	16 (5.2%)	5 (1.6%)

(ref. p. 68, 69, 70, vol. 30, ISS)

Case histories and patient ID numbers were provided in the ISS of 2 patients who increased PR interval by 60 msec. and 5 patients who increased the QTc by 60 msec. or more after the rest Myoview dose (highlighted in table above). These histories included concomitant medications and underlying disease states, as well as associated ECG findings. No associated arrhythmias were seen, and none of the ECG changes were reported as adverse events. All QTc increases >60 msec occurred after the low dose of Myoview. The highest QTc rise was 160 msec (MYO-303 subject #044-0013), a 54-year old female with chest pains, with anteroseptal Q waves and non-specific ST-T changes at baseline. Review of the case report tabulations (CRT's) (vol. 71, p. 40-42) for this patient indicated the QTc to rise from 240 to 400 msec at rest, PR from 120 to 160 msec, and no significant QTc changes during stress, values ranging from 405 to 436 msec. Vital signs did not change appreciably during rest, and appropriately rose during three stages of exercise. Medications included verapamil for migraine, alprazolam and dicycloverine for irritable bowel, fexofenidine for allergies, glimepiride for diabetes, nizatidine for hiatus hernia and salbutamol for asthma. No associated findings were seen to suggest a causal role of Myoview in the QTc increase. Review of CRT's (Vol. 69, 71) for the other four patients with QTc rises >60 msec (#013-0004: 94 msec, #013-0011: 135 msec, #044-0002: 81 msec, #044-0016: 95 msec) likewise indicated no associated findings to arouse suspicion for a role of Myoview in these changes.

c. General Comments and Conclusions: ECG Data

No obvious trends were noted in the ECG database to suggest a causal role for Myoview in prolongation of the QTc, arrhythmias or other significant alterations in the ECG. This is in agreement with the ECG safety profile for Myoview found in the original approved NDA and efficacy supplement SEI-003 for pharmacologic stress approved in December of 2001.

5. Physical Examination

A limited cardiopulmonary physical examination was performed within 10 minutes of the start of treadmill exercise and, on the day of the MUGA exam, within 10 minutes of injection of the [redacted] labelled red cells. A neurological or MMSE exam was not conducted.

For the general physical examination, results were reported for individual studies, and discussed in the ISS. Review of the individual subject data listings for each study did not reveal any trends to suggest Myoview as a cause for alterations in the physical exam.

D.5.d. Overall Adequacy of Safety Testing

The safety database for Myoview SEI-013 (336 patients overall) encompasses 2 completed Phase 3 studies. A 4-month Safety Update was submitted 120 days after sNDA submission, and is reviewed in Appendix #2. This discussion pertains to the database at the time of original sNDA submission. This section addresses the *adequacy* of the database, while recommendations are discussed in Sections D.5.a and D.5.f: Reviewer's Safety Assessment, Comments and Recommendations.

The safety findings have been presented in detail in Section D.5.c. No deficiencies in the adequacy of the database are evident. In the opinion of this reviewer, monitoring and/or reporting of safety was satisfactory in both studies. In the opinion of this reviewer, testing in MYO-301 and 303 was adequate to recommend approval of the supplement on the basis of safety.

D.5.e. Safety Findings from the Submitted Literature

The safety database for the two clinical trials MYO-301 and 303 (336 enrolled patients overall) has already been discussed. In addition to the trials conducted by the sponsor, 22 articles from the literature were submitted as references, all of which addressed Myoview as an agent for evaluating LV function. These were reviewed for their potential value in supporting efficacy (Section D.4.d). All of the articles investigated Myoview in the human.

The 22 articles were searched for reports of adverse events, vital signs, ECG's or clinical laboratory tests. No specific safety plan was described in any of the papers, though no serious AE's or significant ECG changes were reported in any of the submitted articles. In none of the articles was human dosimetry presented or discussed.

D.5.f. Reviewer's Safety Conclusions and Recommendations

The adverse event profile for Myoview in SEI-013 is similar to that for the original Myoview NDA, with chest pain, ST-T wave changes on the ECG and nausea being the most commonly reported. All of these occurred during treadmill exercise and were attributed to the underlying heart disease and stress. Review of vital signs and ECG data also indicate the changes seen to reflect exercise stress or the underlying disease process in cardiac patients, without evidence for a causal role for Myoview.

No major concerns were raised during review of the safety of Myoview in the two GSPECT studies. No evidence that would attribute the serious AE's and withdrawal to Myoview was found.

Recommended action for safety: APPROVAL

Recommendations to address safety concerns: None

Labeling recommendations:

No changes are recommended from a safety perspective. Changes in the proposed labeling are discussed in Dosing and Administration Issues (Section #D.6) and Conclusions, Recommendations and Labeling (Section #D.8).

D.6. Dosing and Administration Issues

The proposed revised labeling (vol. 1, pp. 27-38) calls for a dose of 5 to 33 mCi (185–1221 mBq) of Myoview per injection of a 2-day rest-stress study. For a single-day protocol, 5 to 12 mCi (185-444 mBq) is recommended for the first dose, and 15-33 mCi is recommended for the second injection. The above change in the dose of Myoview proposed here represents an *increase in the upper limit for the first dose of a 1-day protocol from 8 to 12 mCi.* No reasons for increasing this dose were mentioned, including the use of GSPECT in the imaging protocol. However, in the two pivotal studies, the low rest dose ranged from — mCi (mean 10.3 mCi); high rest dose from — mCi (mean 18.1 mCi); stress dose from — mCi (mean 22.9 mCi). The mean low rest dose is clearly in excess of the approved range of 5 to 8 mCi. (see Section #5.b: Demographics and Extent of Exposure).

The approved labeling for Europe, Canada and Japan was included in the submission. Table #6.a.1 below lists the currently approved doses for the above countries and the United States. None of the current labels specifically mentions using a 2-day protocol:

TABLE #6.a.1: Myoview Approved Doses: Foreign and U.S. Labeling

Country	1-day first dose	1-day second dose	Each dose: 2-day
Europe	5-6.8 mCi (185-250 mBq)	13.5-20.3 mCi (500-750 mBq)	Not indicated in current labeling
Canada	5-8 mCi (185-300 mBq)	15-24 mCi (550-900 mBq)	
Japan	5-20 mCi (185-740 mBq)	10-20 mCi (370-740 mBq)	
United States	5-8 mCi (185-296 mBq)	15-33 mCi (555-1221 mBq)	

(ref. vol. 26, pp. 230-272)

The recommendation of this reviewer is for the applicant to stay within the original approved dose limits for the first injection of the 1-day protocol: 5 to 8 mCi (185 to 296 mBq). The recommended second dose for a 1-day protocol of 15 to 33 mCi is unchanged from the original label and is satisfactory. For the 2-day protocol, the proposed label dose of 5 to 33 mCi for each injection is satisfactory, but the applicant must specify the 2-day protocol in the label (See Labeling Review: Section D.8.c).

D.7. Use in Special Populations

This section of the review discusses safety and efficacy of Myoview as broken down by the key demographic factors of gender, age, weight, height and race. This section also addresses the Request for Waiver of Pediatric Studies submitted by the applicant on 17 September 2002.

D.7.a. By-gender Analyses of Efficacy and Safety

A subgroup analysis by gender was conducted with respect to both efficacy and safety of Myoview. Among the 336 patients enrolled in the two trials, 220 were male (65.5%) and 116 female (34.5%). The higher percentage of males in the patient population reflects the higher incidence of known or suspected heart disease in males.

1. By-gender Analysis of Efficacy (ref. p. 63, 64 vol. 27)

A by-gender breakdown was provided for the combined efficacy data for MYO-301 and 303, as well as each study. In the combined efficacy population, there were 195 males (65.7%) and 102 females (34.3%). The proportion of patients with an abnormal LVEF (<50%) as measured by MUGA was higher in males (50.7% versus 26.3% for females). The mean LVEF, as measured by the truth standard MUGA exam, was lower for males (47.8%) than females (56.1%). Among 60 patients with high LVEF values (>65%), 44 were females (73.3%). It is in this population where overestimation of LVEF by GSPECT due to small heart size is most likely. For an *abnormal* LVEF, the overall sensitivity of Myoview GSPECT was higher in males (85.7% versus 77.5% for females), but specificity was higher in females (90.1% versus 74.8% for males). A by-gender breakdown of efficacy with respect to wall motion was not made. As noted above, the majority of patients enrolled in the two studies were males, in whom the incidence of heart disease is greater.

2. By-gender Analysis of Safety

A by-gender breakdown for adverse events was provided in the ISS, pooled for the two studies. Review of the data listings for adverse events indicated AE's to occur with nearly identical frequency in the two sexes (11.6% for males and 11.5% for females). Within each COSTART body system, the numbers under each AE classification were too small to make any statistical conclusions, but no obvious differences between the sexes were seen. Breakdowns by gender were not provided for vital signs or ECG parameters; review of data listings did not indicate any trends to suggest gender effects on these parameters.

D.7.b. Racial and Ethnic Considerations

Subgroup analyses by race/ethnic group were not provided for neither safety nor efficacy of Myoview in this submission.

D.7.c. Age, Weight and Height

For the subgroup analysis by age, patients were divided into those <65 years and those 65 years or older. Too few patients over 80 years of age (13) were enrolled to separate them out for analysis. In general, the older patients had more severe heart disease, with abnormal LVEF by MUGA seen in 58 of 143 patients 65 years of age or older (40.6%) and in 68 of 186 patients under 65 years (36.6%). For efficacy, the sensitivity of Myoview GSPECT for detecting an LVEF abnormality was greater in those 65 or older (91.2%) than in the <65 year age group (77.7%). The specificity for LVEF was also greater in the older patients (85.9% versus 78.3%).

No specific analyses of efficacy were made on the basis of weight or height. For safety, a logistic regression model was applied, using weight or height as the independent variable and AE incidence as the dependent variable. Neither factor had a predictive effect on the incidence of AE's.

D.7.d. Pediatric Considerations: Waiver Request

Myoview was not studied in the pediatric age group (0-18 years) and a pediatric indication for this drug is not being sought in the current submission. NDA #20-372 SEI-013 did not include a Request for Waiver of Pediatric Studies for this indication according to 21 CFR 314.55(c)(2). On page 2 of Volume 1, the applicant indicates that they submitted on July 17, 2001 a Waiver of Phase 4 Commitments to perform pharmacokinetic studies of tetrofosmin in adults and adolescents to define the drug's metabolic profile and possible dose adjustments for pediatric patients, and that the Waiver also applies to the current submission. In this Waiver, the applicant indicated their opinion that the above PK studies were not justified, stating that it was not feasible to detect tetrofosmin and its metabolites in body fluids using existing analytical methods. The submission included a non-clinical section with articles on the pharmacokinetics and metabolism of tetrofosmin. To address concerns regarding pediatric dosing, the applicant included review articles on pediatric dosing and adjustment methods. This submission does not, however, constitute a Request for Waiver of Pediatric Studies under the Pediatric Rule.

In the Approval Letter of November 23, 2001 (for the pharmacologic stress supplement SEI 003), receipt of the July 17 package was acknowledged, and it was stated that it would be responded to under separate cover, and that the requirement for the above PK studies was still in effect.

On September 17, 2002 a formal Request for a Full Waiver of Pediatric Assessment for this NDA supplement was submitted. In this letter, the applicant reiterates that it is not feasible to detect tetrofosmin and its metabolites using current analytical methods, and suggests that the current knowledge and clinical practice of pediatric dose adjustment (described in the July 2001 submission) be applied to Myoview when used according to the new indication. The applicant then states that adjustment of dose based on body weight and body surface area are the most valid scientifically. Selection of a particular dose will also be based on extrinsic factors such as gamma camera sensitivity, movement of the patient, sedation and, of course, the recommended adult dose. A dose range of 0.14 to 0.54 mCi (5-20 MBq) per kg body weight was recommended in the July 2001 submission (vol. 2, p. 19). The applicant then concludes that, on the basis of sufficient guidance being available for pediatric dosing, an additional clinical study is not warranted.

Under 21 CFR 314.55.9(c)(2)(i), a full waiver of pediatric requirements is justifiable if the drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of such patients. However, the assessment of ventricular function may be indicated in children, and the submission of NDA #20,372 SEI 013 has triggered the Pediatric Rule. Therefore, the applicant will need to submit a Pediatric Plan for the use of Myoview to assess ventricular function.

D.8. Conclusions, Recommendations and Labeling

D.8.a. Overall Analysis of Risk/Benefit

A discussion of risk/benefit for Myoview as used to evaluate ventricular function should focus first on the potential benefit from using the drug: does it ultimately help the physician to reach a diagnosis? The *Guidance for Industry: Developing Medical Imaging Drugs and Biologics* (June 2000) offers some guidelines with respect to answering this question, and states that indications for a medical imaging drug fall into 4 general categories as listed below. The indication proposed in the label for Myoview (assessment of ventricular function) would fit into Category 2.

1. Structure delineation
2. Functional, physiological or biochemical assessment
3. Disease or pathology detection or assessment
4. Diagnostic or therapeutic patient management

The risks of using a medical imaging drug fall generally into two broad areas: 1) the risk of actually administering the drug (toxicity), and 2) the risk of the drug *providing incorrect information* (wrong diagnosis, for example). The above mentioned *Guidance for Industry* emphasizes this point in the risk/benefit discussion. With respect to Myoview, the overall adverse event profile in patients studied to date appears to reflect the use of exercise or pharmacologic stress agents as adjuncts to evaluating myocardial perfusion. For the new indication of ventricular function, the submitted database has demonstrated no appreciable changes in the safety profile of Myoview and is adequate to assure the overall safety of the radiopharmaceutical. The risks of arriving at an incorrect diagnosis can be assessed with further comparison of Myoview scan results with patient outcomes.

The potential benefit of using GSPECT with currently approved myocardial perfusion agents is the possibility of evaluating myocardial perfusion and function in a single study. An additional advantage is the decrease in operator dependency to perform LV ejection fraction measurements (no need for a technologist to generate a ROI about the LV blood pool). GSPECT still depends on reliable edge-detection of the LV endocardial border, but does not rely on a technician to do so.

D.8.b. Overall Approvability

From a clinical perspective, this reviewer recommends an *approval* action for this Myoview sNDA based on efficacy and safety results of the two pivotal studies MYO-301 and 303, as well as additional support from the submitted literature. A subset analysis of efficacy in patients with exercise-induced ischemia is recommended to test the hypothesis of myocardial stunning as a cause for underestimation of ejection fraction by GSPECT performed after exercise stress. Recommended changes in the proposed label are indicated in Section D.8.c below.

D.8.c. Labeling Review (Ref: text of proposed package insert, pp. 41-71, vol. 1: Application Summary)

Recommended changes in the labeling include revision of the rest Myoview dose from 5-12 mCi to 5-8 mCi as indicated in the original label, changing the proposed indication from *ventricular function* to *left ventricular function*, based on the submitted data, and indicating in the clinical trials section that the truth standard MUGA exam was evaluated by an independent panel *who reached a consensus*, and clarification dosing when imaging is done on separate days (5-33 mCi per injection). Additions to the clinical trials section should include the efficacy tables on page 40 of this review (#4.e.1 and 4.e.2, reproduced from the ISE) and a statement that Myoview was evaluated in two pivotal Phase 3 studies in 336 subjects (220 male, 116 female, mean age 60.6 years) being evaluated for known or suspected heart disease and/or ventricular function. The label should also include a statement that 47 adverse events were reported in 38 of 329 subjects (11.6%); four occurred before stress (headache, nausea, anxiety and pneumonia). Events occurring in >1% of the subjects included ECG changes (6 or1.8%) and chest pain (6 or 1.8%), all of which were associated with exercise stress. Nausea was reported in 5 (1.5%) of the subjects.

D.8.d. Recommended Regulatory Action: **APPROVAL.**

E. Signature Section and CC List:

1. S

Nelson B. Arnstein, M.D.
Medical Officer, HFD-160

Date

2. S

Sally Loewke, M.D.
Deputy Division Director, HFD-160

Date

3. S

Patricia Y. Love, M.D., M.B.A.
Division Director, HFD-160

Date

4. CC List:

HFD-160: NDA File
HFD-160: Division File
Division director: Dr. Patricia Y. Love
Division deputy: Dr. Sally Loewke
Project Manager: Patricia Stewart, CNMT.
Statistics: Anthony Mucci, Ph.D.
Clinical reviewer: Nelson B. Arnstein, M.D.

F: Appendices

F.1. Appendix 1: Clinical Correspondences from Applicant since NDA Supplement Submission

Correspondence 1: 8/23/02 SEI-013 SU: 1 volume
120-Day Safety Update

Correspondence 2: 9/17/02 SEI-013 PW: 1 volume
Request for Waiver of Pediatric Studies

F.2. Appendix 2: Review of 4-Month Safety Update

A 4-Month Safety Update (Correspondence #1) was submitted on 8/23/02. The submission contained no additional non-clinical safety information. No clinical studies were conducted by the applicant during the 120-day period covered by the Update. The Safety Update includes a Summary of Post-marketing Experience with a newly revised list of spontaneously reported adverse events, an assessment of 15-Day IND safety reports, and a review of additional published literature. In the Appendices of the submission, tables are provided which list spontaneous AE reports received from 3/1/02 to 7/15/02, changes made to these reports, spontaneous AE counts by WHO-ART preferred term and a database search strategy for the published literature. In the time since approval of the original Myoview NDA, a total of 251 AE's have been cited in 158 spontaneous reports submitted to the applicant up to July 15, 2002. Of these, 24 reactions were cited in 15 reports during the period 3/1/02 to 7/15/02. Among these, 3 represented serious adverse events; narratives for these patients were submitted with the Update. During the first 6 months of 2002, approximately 1,180,000 patients have been exposed to Myoview worldwide. The sources for spontaneous AE reports is the global pharmacovigilence database for Amersham Health; for exposure to Myoview, sales figures for the first 6 months of 2002. A search of available published literature from 3/1/02 to 7/15/02 cited 2 new articles which did not provide any new safety information pertaining to Myoview.

F.2.a. Summary of Spontaneously Reported Adverse Events

If adverse events associated with pharmacologic stress are excluded, a total of 192 spontaneous AE's have been reported to the applicant since original NDA approval; these are listed in the table below. The period covered is 2/9/96 to 7/15/02.

TABLE #F.2.a: Spontaneously Reported AE's Not associated with Pharmacologic Stress from 2/9/96 to 7/15/02 by Body System: N

ADVERSE EVENT	Count (192 grand total)
Body as a whole: General	66
Allergic reaction	30
Pain	7
Fever	5
Anaphylactoid reaction	4
Chest pain: non-cardiac	4
Edema: mouth	3
Edema	2
Back pain	2
Rigors	2
Temperature changed sensation	2
Asthenia	1
Malaise	1
Anaphylactic shock	1
Pallor	1
Hot flushes	1
Cardiovascular	**11**
Hypotension	4
Hypertension	2
Bradycardia	1
Cardiac arrest	1
Palpitation	1
Tachycardia	1
Arrhythmia	1
Respiratory	**9**
Dyspnea	4
Rhinitis	2
Cough	2
Stridor	1

Peripheral vascular	**5**
Flushing	2
Phlebitis	1
Vasculitis	1
Vein disorder	1
Gastrointestinal	**22**
Nausea	9
Vomiting	5
Diarrhea	3
Dyspepsia	2
Stomatitis	1
Abdominal pain	1
Rectal bleeding	1
Urinary system	**2**
Urinary tract infection	1
Urine abnormality #	1
Skin and appendages	**33**
Rash	14
Erythematous rash	5
Urticaria	4
Pruritus	4
Pustular rash	2
Alopecia	2
Increased sweating	1
Hair discoloration	1
Musculo-skeletal	**1**
Arthrosis	1
CNS, Peripheral Nerves	**22**
Headache	8
Dizziness	6
Paresthesia	2
Convulsions	1
Involuntary muscle contractions	1
Hypoesthesia	1
Abnormal gait	1
Dysesthesia	1
Speech disorder	1
Psychiatric	**6**
Confusion	2
Dysorexia	1
Somnolence	1
Anxiety	1
Agitation	1
Special senses	**14**
Taste perversion	10
Vision abnormal	3
Conjunctivitis	1
Secondary terms	**1**
Burns to eye	1

* WHO-ART Body System # Laboratory changes considered as AE's
(Derived from Appendix 7.3 page 18, Safety Update)

During the period from March 1 to July 15, 2002, a total of 15 reports citing 24 adverse reactions were submitted to the applicant. Among these, 11 reports citing 16 adverse reactions in patients undergoing imaging at rest or exercise (*not pharmacologic*) stress were retrieved by the applicant during this period. These are listed in Appendix 7.1 of the submission and reproduced in Table # F.2.b on the next page:

TABLE #F.2.b: Spontaneously Reported AE's Not Associated with Pharmacologic Stress from 3/1/02 to 7/15/02 by Body System (Derived from Appendix 7.1 pp. 15-16, Safety Update)

ID#	Age, sex	Country	WHO-ART Preferred Term	Latency	Stress type	Outcome
	77 F	USA	Bradycardia*	10-20 min.	No Pharm. Stress	Death
	45 M	USA	Anaphylactic shock*	Early	Rest	Recovered
	56 M	USA	Tachycardia*	Early	Exercise	Recovered
	52 F	JAPAN	Allergic reaction	?	Exercise	Recovered
	69 F	NL	Headache	90 min.	No Pharm. Stress	Recovered
	66 F	NL	Nausea	90 min.	No Pharm. Stress	Recovered
	84 F	USA	Abdominal pain	4-5 min.	Rest	Recovered
			Chest pain			
			Allergic reaction			
	? F	USA	Dyspepsia	1 day	Rest	Recovered
	55 F	Canada	Paresthesia	24 hours	Rest	Recovered
			Eye burns			
			Headache			
			Pain			
	55 F	USA	Allergic reaction	Early	No Pharm. Stress	Recovered
	36 F	USA	Hair discoloration	?	No Pharm. Stress	Recovered

Three new serious adverse events (including 1 death) were reported during the 4-month interval covered by this Update (marked with * in the table above), and submitted as 15-Day IND safety reports. Brief narratives below are derived from pages 9-10 of the Update:

- Patient # [redacted] (death): This 77-year old female presented to the ER with substernal chest pain radiating to the jaw. She denied prior cardiac disease, but had a history of diabetes, arthritis, hip and knee arthroplasties and cholecystectomy. Medications included Vioxx (rofecoxib) and Tums. ECG in the ER was normal, but she was given nitropaste and lidocaine, and admitted. The next day, she was given an IV dose of 12-13 mCi of Myoview. Ten to 20 minutes later she was found to have a drop in the heart rate on the telemetry monitor. The nurse discovered the patient to be in the room, face down on the floor, with no pulse. Attempts to revive her failed; the cause of death could not be determined.

- Patient # — (anaphylactic shock): The patient is a 45 year old male who experienced anaphylactic shock. In an imaging clinic, he received a rest dose of 10 mCi of Myoview followed by saline, to rule out coronary disease. Shortly after dosing, he turned pale, red-faced and developed shallow breathing. His head slumped over and eyes were deviated. Blood pressure was 140/70, but the patient lost consciousness and became non-responsive. One minute after administering nasal ammonia, the patient revived and was alert a few minutes later. Vital signs were stable throughout the episode; his blood pressure slowly returning to a baseline 110/60. There were no ECG changes or focal neurological deficits. He was transferred to the emergency room for further evaluation. No further information was provided in the narrative.

- Patient # — (tachycardia): This 56-year old male underwent Myoview perfusion scintigraphy to evaluate for possible myocardial ischemia as a cause for indigestion. He received a 10 mCi rest dose, followed by 30 mCi for the stress exam. The stress dose was given less than 1 hour after the rest dose. At an unspecified time after treadmill stress, he experienced an extremely rapid heart rate and 3 episodes of heart stoppage of 6 seconds each. A pacemaker was implanted 26 October 2001 with complete recovery.

Adverse events reported in this Update have been consistent with those in the original NDA, and no new safety concerns have been raised. The incidence of AE's within each body system category has also not changed substantially.

F.2.b. Conclusions from Safety Update

The data submitted in this Update, along with that submitted in the efficacy supplement #SEI-013 have demonstrated a risk commensurate with that presented in the original NDA. None of the events since March 1, 2002 have triggered any recommendations to change the current approved label as well as the proposed label in the Supplement on the basis of safety.

F.2.c. Package Insert

Suggested revisions in the proposed label have been discussed in the Clinical Review in Sections D.6 and D.8. No changes on the basis of this Safety Update are recommended.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Nelson Arnstein
10/3/02 06:07:41 PM
MEDICAL OFFICER

Sally Loewke
2/27/03 06:30:26 PM
MEDICAL OFFICER
I agree with Dr. Arnstein's recommendation. Please see my review for additonal comments