

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

**APPLICATION NUMBER
20-372/SE1-003**

Medical Review(s)

**a clinical review of
MYOVIEW
(Tc-99m tetrofosmin) Efficacy Supplement
Response to Approvable Letter of 21 December 1999**

NDA #20,372: SEI 003 AZ

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HFD-160
U.S. Food and Drug Administration**

3 November 2000

1: General Information and Abstract:

1:1 CLINICAL REVIEW OF NDA

#20,372 S003 AZ: Response to Approvable Letter

Submitted: 6/23/00

PDUFA Goal Date: 12/26/00

Nelson B. Arnstein, M.D.
Medical Officer, HFD-160
Review assigned: 6/30/00
Review completed: 11/3/00

1:2 Drug names: Generic: Technetium-99m tetrofosmin

Trade name: Myoview

1:3 Sponsor: Nycomed Amersham Imaging

101 Carnegie Center

Princeton, N.J. 08540-6231

1:4 Pharmacologic Category: Diagnostic radiopharmaceutical

1:5 Proposed Indication: (quote from the Sponsor) "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 areas of reversible myocardial ischemia in the presence or absence of infarcted myocardium.

1:6 Dosage Forms and Route of Administration: 5 to 8 mCi during pharmacologic stress, and 15 to 24 mCi at rest by intravenous injection

1:7 NDA Drug Classification: 1S

1:8 Important Related Drugs: Pharmacologic stress agents: Dipyridamole, adenosine
Myocardial perfusion agent: Thallium-201, Tc-99m sestamibi

1:9 Review Team:

Project Manager: Patricia Stewart

Statistics: Antonio Mucci, Ph.D.

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Clinical team leader: Ramesh Raman, M.D.

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1:10 Abstract:

Myoview is a Tc-99m based myocardial perfusion imaging agent currently approved under NDA #20,372 for use in conjunction with rest and exercise stress testing. In the current submission, the Sponsor is providing a Response to the Approvable Letter of 21 December 1999 for Supplement SEI 003, seeking to expand the indications for Myoview to include myocardial perfusion scintigraphy under pharmacologic stress conditions.

The Approvable Letter indicated that the submitted studies and literature articles in SEI 003 had several protocol design flaws which limited their usefulness or confounded the analysis in support of the proposed indication. These included for the pivotal studies P53-006 and PR95-302 1) consensus reading of images, 2) enriched study populations and 3) vessel-level analyses of efficacy less robust than would be expected in such an enriched population. The letter requested an independent blinded re-read of images from the two trials to address issue #1, while a new study in an "all-comers" population would address issue #2. Resolution of issue #3 would depend on results of the new blinded read.

In a subsequent meeting with the Division on 2/17/00, the Sponsor suggested that results from the blinded re-read alone may be sufficient to support an interim, restricted indication for patients *with known or suspected CAD* undergoing pharmacologic stress. The Division communicated to the Sponsor that results of the re-read would need to be more robust (on a vessel level) than the consensus data for the indication to be considered. The current submission, intended to provide this data in support of the restricted indication, includes 1) reports of the blinded re-reads from the pivotal trials (Reports 2954A and 2955A) and 2) selected articles from the literature (with review) published before and since SEI 003 submission.

Review of Reports 2954A and 2955A has revealed a number of deficiencies which reduce the supportive value of their results, even for the limited indication:

- 1) Sensitivity for CAD detection was less robust for new blinded read than for original consensus read on a subject level, and for most individual coronary arteries (both reports)
- 2) Sensitivity for CAD detection was lower for Myoview than for Tl-201 (Report 2955A)
- 3) Specificity on subject level irrelevant for Report 2955A as all subjects have CAD
- 4) Overall vessel-level sensitivities lower than subject-level sensitivities (both reports)
- 5) Sample sizes extremely small (especially Report 2955A)
- 6) Poor scan quality as judged by blinded readers (esp. Report 2955A)

The Sponsor has stated that results of the new blinded reads were comparable to results from the pivotal exercise-stress studies in the original NDA. The use of unblinded readers, planar images and different endpoints (% correct diagnoses of ischemia and infarction) in the earlier studies makes this comparison invalid.

The literature submitted includes 15 articles published since submission of SEI 003. Though each was based on prospective study design, defined populations, objective endpoints and use of blinding or randomization, none met all FDA Effectiveness Guidance criteria for published articles, and each had one or more flaws (including use of non-approved pharmacologic stressors) excluding it from consideration.

In summary, the efficacy data provided in the current submission (blinded re-read reports #2954A and 2955A as well as selected articles in the medical literature) are not adequate to support the limited indication sought by the Sponsor, for reasons indicated above. This reviewer recommends the application remain approvable pending the completion of a new study with data to show that Myoview is not only efficacious in the limited population with known or highly suspected CAD, but also "all-comers" including those at lower risk of having the disease.

The submitted Safety Update has listings and tables of adverse events since approval of the original Myoview NDA from three sources: spontaneous reporting, ongoing U.S. clinical trials and ongoing foreign clinical trials. A total of 168 events have been reported (including 9 deaths and 96 serious AE's). Though it is unlikely that any of the deaths and serious AE's were directly attributed to Myoview, further details on these cases are needed to confirm this, and were requested of the Sponsor on 3 October 2000.

Overall Recommendation: **APPROVABLE (AE)**

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3: Material reviewed: NDA #20,372 response archival copy, volumes: 1-16

- Vol. 1: pp. 1-104: Cover Letter, Form FDA 356h, User Fee Cover Sheet, Debarment Certification, Financial Disclosure Statement, Reviewer's Guide to the Resubmission, Index, Draft Revised Labeling, Application Summary, and Foreign Labeling
- Vol. 2: pp. 1-232: Study Report 2954A: Addendum A (Protocol P53-006)
- Vol. 3: pp. 1-292: Study Report 2954A (continued)
- Vol. 4: pp. 1-91: Training materials, CRF for blinded readers, Study Report 2954A
- Vol. 5: pp. 357-742: Original Study Report 2954 (Protocol P53-006)
- Vol. 6: pp. 1-376: Study Report 2955A: Addendum A (Protocol PR95-302)
- Vol. 7: pp. 1-365: Study Report 2955A (continued)
- Vol. 8: pp. 1-108: Training materials, CRF for blinded readers, Study Report 2955A
- Vol. 9: pp. 1103-1343: Original Study Report 2955 (Protocol PR95-302)
- Vol. 10: pp. 1-69: Addendum A to Integrated Summary of Efficacy
- Vol. 11: pp. 2-378: Original Integrated Summary of Efficacy
- Vol. 12: pp. 1-96: Addendum A to Integrated Summary of Safety
- Vol. 13: pp. 2-255: Original Integrated Summary of Safety
- Vol. 14: pp. 1-285: Summary of Published Literature, Copies of Articles
- Vol. 15: pp. 1-302: Literature Articles Cited
- Vol. 16: pp. 1-302: Literature Articles Cited (continued)

Correspondence #1: 8/1/00 Request for Full Pediatric Waiver and Response to Phase 4 Commitment

Correspondence #2: 10/13/00 Response to Draft Statistical Comments of 3 October 2000

Correspondence #3: 10/25/00 Response to Draft Clinical Comments of 3 October 2000

4: Description of Clinical Data Sources and Regulatory History:

The efficacy database for the resubmission of the NDA #20,372 supplement is provided by the blinded re-read of 2 clinical trials conducted under IND [] and selected reports from the medical literature. The pivotal trial re-reads for Study #P53-006 and PR95-302 are reviewed in Section #5 along with the literature references submitted. Efficacy results of the re-reads together with studies in the literature will also be discussed in Overview of Efficacy (Section #6).

4:1 Data sources in support of efficacy:

4:1:1 Report #2954A (Blinded re-read for Study P53-006) Vols. 2-3 of submission

4:1:2 Report #2955A (Blinded re-read for Study PR95-302) Vols. 6-7 of submission

4:1:3 Literature: (Submitted references and review of selected articles) Vols. 14-16 of submission

4:2 Regulatory History:

NDA #20,372: Myoview (Tc-99m tetrofosmin for Injection) was originally submitted in June of 1993. The application was approved in May 1995 for Myoview to be used to detect myocardial ischemia in the presence or absence of myocardial infarction, using exercise stress. In February of 1999, an Efficacy Supplement (sNDA #20,732 SEI 003) was submitted to the Agency seeking to expand the Myoview indication to include pharmacologic stress. The supplement included reports from 5 clinical trials (including 2 pivotal studies: P53-006 and PR95-302) conducted by the sponsor and 7 articles from the peer-reviewed medical literature. No changes were made in the formulation; nor were additional pre-clinical data submitted.

Review of SEI 003 was completed in December of 1999 with an Approvable action. The Action Letter indicated that the submitted studies and literature articles in SEI 003 had several design flaws which limited their usefulness in support of the new indication. These included for the pivotal studies 1) consensus blinded reads of the images, 2) an enriched patient population and 3) a vessel-level analysis of efficacy which was less robust than would be expected in an enriched population. The letter recommended an independent blinded re-read of images from the two trials to address the first issue, while a new study in an "all-comers" population would address the second issue. Resolution of the third issue would depend upon results from the new independent blinded read.

The sponsor responded to the letter by requesting a meeting with the Division with a proposal that the blinded re-read alone could be sufficient to support an interim, restricted indication for patients *with known or suspected CAD* undergoing pharmacologic stress. At the meeting, which was held 17 February 2000, the Division communicated to the sponsor that results of the re-read would need to be more robust (on a vessel level) than the consensus data for the indication to be considered. The current submission provides this data in support of the new restricted indication. The protocol for the blinded re-read was submitted on 22 March 2000; clinical and statistical comments from FDA were sent to the sponsor on 30 May and 25 May 2000, respectively. The current submission includes the Sponsor's response to these issues (Vol. 1, pp. 015-018). On 27 June 2000, SEI 003 AZ was formally accepted for filing, though the Division did not necessarily agree that the submission constitutes a complete response.

With respect to issue #2 above, the sponsor has submitted under separate cover a protocol for a new study _____ evaluating Myoview in an "all-comers" population undergoing pharmacologic stress. This is currently under review in the Division, but is not considered a part of this Response. According to the sponsor, the results of this study will be submitted as a new NDA supplement in mid- to late 2001.

The response also includes a request for deferral of pediatric studies with Myoview and pharmacologic stress, and a statement that Phase 4 commitments for a pharmacokinetic evaluation of pediatric subjects are currently being addressed.

5: Clinical Studies and Published Literature:

5:1 Introduction

Table #5.1 below summarizes the design features and overall sensitivity/specificity results for the new Study Reports #2954A and 2955A. Table #5.2 on page 6 compares the salient characteristics of the new blinded re-read with the original reads for Studies P53-006 and PR95-302.

Table #5.1: Trials in Efficacy Database

TRIAL	P53-006 Study Report 2954A	PR95-302 Study Report 2955A
Study design: blinded read	3 independent readers	3 independent readers
Study objectives	Sensitivity and specificity for detecting CAD on a subject and vessel basis	Comparison of Tl-201 and Myoview for sensitivity in detecting CAD on a subject and vessel basis
Truth standard	Coronary angiography	Coronary angiography
Comparator (other than angiography)	None	Tl-201 (3 mCi) + dipyridamole
No. of subjects	46 to 49 evaluable	19 to 21 evaluable
CAD criteria	≥50% occlusion Left Main: ≥70% occlusion	≥50% occlusion Left Main: ≥70% occlusion
Sensitivity (range among 3 readers)	47.4% to 83.3% on subject level 29.6% to 76.2% on vessel level	70.0% to 76.2% on subject level for Myoview 31.3% to 71.4% on vessel level for Myoview
Specificity (range among 3 readers)	71.4% to 100.0% on subject level 50.0%-100.0% on vessel level	Not specified on subject level* 33.3% to 100.0% on vessel level for Myoview
Comments	Graded score (0-4) of 17 cardiac segments Small sample size	Graded score (0-4) of 17 cardiac segments. Very small sample size

* Specificity can not be computed due to 100% CAD prevalence in Study PR95-302 population

5:2 Review of Blinded Re-read for Studies P53-006 & PR95-302: (Reports 2954A & 2955A)

P53-006: "An Open-label Study to Evaluate the Use of a One-day, Dipyridamole-Tc-99m Tetrofosmin Imaging Protocol in the Assessment of Coronary Artery Disease".

PR95-302: "Comparison of Dipyridamole-201 Thallium with Dipyridamole-Tc-99m Tetrofosmin SPECT Imaging in Patients with Angiographically Confirmed Coronary Artery Disease".

5:2:1 Protocols for Blinded Re-read

5:2:1:1 Background

On 22 March 2000, the Sponsor submitted two protocols for blinded re-reading of Tc-99m tetrofosmin images (serial #SEI 003 BM); one for each of two Phase 3 trials in the original efficacy supplement seeking a pharmacologic stress indication for Myoview (P53-006 and PR95-302). In Study PR95-302, Tl-201 images are also interpreted and used as a comparator; otherwise the protocols are nearly identical. Clinical and statistical comments for the blinded read protocols were sent to the Sponsor in May of this year; the protocols submitted with this Response address these issues and questions.

The protocols call for an independent blinded re-reading of existing images without enrolling new study subjects. Table #5.2 on the next page summarizes design features of the original consensus read for each study and the new independent blinded re-read for both studies.

standard cardiac axes: Short Axis, Vertical Long Axis and Horizontal Long Axis. The data was subjected to quantitative analysis and representative images (polar maps) generated. A total of 58 rest/stress image sets were interpreted. Original digital image data were not recoverable for 10 subjects in this study.

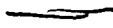
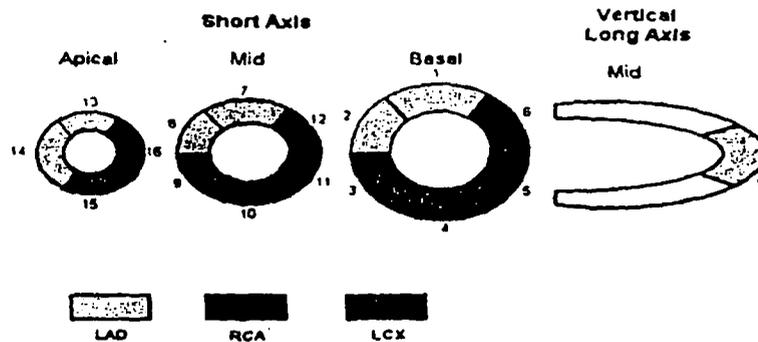
- b) Randomization and blinding: All 58 evaluable image sets were to be randomized so that Myoview images for a given subject were not presented to the readers at the same time. Readers were to be blinded to patient identity, diagnosis, gender, clinical information and the study protocol.
- c) Training of blinded reviewers: The 3 readers were independent attending nuclear cardiologists not affiliated with the Sponsor, not involved in image acquisition and not affiliated with the institutions where the images were acquired or prepared for the blinded read. To familiarize him/her with the workstation, each reviewer was given a chance to read 10 trial sets of images, including normals and abnormal in a random sequence. They were evaluated for consistency (including matching defects across the 3 axes). The materials were not submitted with the original protocol, but with the subsequent Response to the Approvable Letter.
- d) Presentation of images to blinded readers: Reconstructed slices and quantitative images (polar maps) were presented to each of the 3 readers in a format standardized by the American College of Cardiology (ACC) and Society of Nuclear Medicine (SNM). This included the slices presented in the 3 cardiac axes and a polar map based on the quantitative analysis of these images. The images were presented to the readers in a linear gray-scale, but could be switched to color at the discretion of the reader. In addition,  planar images of the heart at rest and stress were shown for interpreting patient motion, breast and diaphragmatic attenuation and overall image quality. To be consistent with current clinical practice, each of the 58 images was presented to the readers and read as rest/stress pairs. The readers were able to change no data acquisition or processing parameters, image displays, color scales or filters.
- e) Segmentation and scoring of images: A 17-segment myocardial model, one of 2 presented in the ASNC guidelines, was used. This divides the polar map into six 60-degree segments each from the basal and middle short-axis slices, four 90-degree segments from the apical short axis slice, and a single apical segment from the vertical long-axis slice. The model is portrayed in Figure #1 on the next page. Segments were grouped into LAD, LCx and RCA coronary artery territories, also according to ASNC guidelines. Each segment is scored from 0 = normal uptake to 4 = absent uptake. Segments were graded as normal, reversible, partially reversible or fixed. "Reverse redistribution" was considered normal. A single abnormal segment qualified a scan as abnormal. The scans were judged as to image quality (diagnostic or non-diagnostic), using the rotating images as well as the reconstructed slices to help assess patient motion, technical artifacts, attenuation, count rate, etc.

Figure #5.1: 17-Segment Model (Ref. p. 19, vols. 2 and 6 of submission)



17 Segment Model

LAD: Segments 1,2,7,8,13,14,17

LCx: Segments 5,6,11,12,16

RCA: Segments 3,4,9,10,15

- f) Data entry into CRF: Each blinded reader completed a Case Report Form (CRF) whose data was sent to the Sponsor electronically after checking by a monitor who documented the CRF completeness as well as the overall conduct of the blinded read.
- g) Statistical methods: A separate protocol was submitted as a Statistical Analysis Plan. This described the 17-segment model, coronary territories, scoring system for each segment, definition of normal/abnormal scans and a definition of CAD ($\geq 50\%$ stenosis in LAD, LCx or RCA, or $\geq 70\%$ in the LM). To assess intra-reader variability, 10% of the study images were presented to the readers twice (at random, at separate times). Only the first reading was included in the efficacy analysis. By subtracting the defect scores for a given segment at rest from that obtained at stress, one can compute the "reversibility" score, a measure of stress-induced ischemia. Analysis of "reversibility" of Myoview images was not included in the Plan.
- h) Efficacy endpoints: The primary endpoint was the number of angiographically abnormal subjects correctly assessed as having abnormal perfusion on the Myoview pharmacologic stress study (sensitivity). Secondary endpoints included a similar analysis on a by-vessel basis, and the number of subjects correctly assessed as having single- or multivessel CAD Myoview with pharmacologic stress. The tracer was also evaluated on a per-subject and per-vessel basis as to defect extent (number of abnormal segments) and sum defect score (total of segmental defect scores).

5:2:1:3 Protocol Design and Description: PR95-302

The blinded read protocol for Study PR95-302 is similar to that for P53-006, except that the study includes TI-201 images used as a comparator. TI-201 scans were interpreted and correlated to angiography in the same manner as Myoview scans. The same 17-segment model and 0 to 4 scoring system for perfusion defects were utilized.

"Reversibility" of defects was not separately analyzed in P53-006 but was studied in PR95-302. The reason for this was that no standard of truth is available for "reversibility", a functional process without an angiographic correlate. Instead, agreement

analysis was used to compare reversibility assessments using TI-201 and Myoview. Criteria for diagnosing "normal", "ischemia" and "infarct" or "scar" on a segment, vessel and subject level were specified on page 20, vol. 6 of the submission:

For a given segment, "reversibility" was defined in terms of the difference between stress and rest scores. The range is 4 for completely reversible to 0 for irreversible defects. Differences of 1, 2 and 3 indicated partially reversible defects. Defects were considered "infarct" if fixed, "ischemia" if reversibility was complete, and both "ischemia" and "infarct" if reversibility was only partial.

On the vessel level, a vessel territory was considered "normal" if all segments within that vessel's distribution were normal, "ischemic" if at least 1 segment was completely or partially reversible, and "infarcted" if at least 1 segment was fixed and no segments were reversible. If one defect in a given vascular territory was fixed and another segment in the same territory reversible, the vessel territory was considered "ischemic".

On the subject level, the subject was "normal" if all vascular distributions were normal, "ischemic" if at least 1 vascular distribution was ischemic; and "infarcted" if at least 1 vascular distribution was infarcted, regardless of the presence of ischemia in the other vessel distributions.

Reviewer's comment: In the clinical section of the submission (p. 20, vol. 6), the above definitions of "ischemia" and "infarction" appear to be different on the subject and vessel levels. On the vessel level, a territory containing a reversible segment is considered to be "ischemic" *whether or not an infarcted segment is present in that same distribution*. A territory was only considered to be "infarcted" if at least 1 segment within that distribution was fixed and *no* segments within were "ischemic". On the subject level, a heart with an "infarcted" vessel territory was considered to be "infarcted" *whether or not other vessel territories in that heart were ischemic*. This is also in contrast to the statistical section of the submission (page 26, vol. 6), which stated that all subjects with an "ischemic" vessel territory were considered "ischemic", *whether or not infarction was present*. Here, the diagnosis of "infarction" on a subject level would only be made in the *absence* of segmental or vessel-level ischemia. Corroboration with the statistical reviewer and the raw data indicate the latter definitions of abnormalities to be the correct ones. Given the current proposed indication for Myoview of "delineation of areas of reversible myocardial ischemia in the presence or absence of infarcted myocardium", the latter criteria for the diagnosis of ischemia on a subject level would be appropriate. To support this claim directly, data indicating the ability of Myoview to *detect ischemia* is needed, rather than sensitivity and specificity data of Myoview for *detection of CAD*, as presented in this submission.

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Table #5.2: Blinded Read Comparisons

#	Item	Consensus read P53-006 Report 2954A	Consensus read PR95-302 Report 2955A	Independent reads (both studies)
1	# studies read (by each reader for independent read)	63 (58 evaluable)	26 (25 evaluable) (52 image sets)	49, 46, 49 (P53-006) 19, 20, 21 (PR95-302)
2	Independent core lab	Yes	Yes	Yes
3	Images reconst. by core lab	Yes	Yes	Yes
4	# blinded readers	2 (3 rd for tie-break)	2 (3 rd for tie-break)	3
5	Indep./consensus read	Consensus	Consensus	Independent
6	Readers indep. of study	Yes	Yes	Yes
7	Readers blinded to protocol	No	No	Yes
8	Image quality assessed	Yes	Yes	Yes
9	No. of segments scored	14	14	17
10	Defect rating: stress	0 (nl) - 4 (absent) 5 (indeterminate)	1 (mild) - 3 (severe) blank = normal	0 (nl) - 4 (absent)
11	Defect rating: rest	0 (nl) - 4 (absent) 5 (indeterminate)	1 (reversible) - 3 (fixed)	0 (nl) - 4 (absent)
12	Mapping to coronary territory	Yes	Yes	Yes
13	Training of blinded readers	No	No	Yes
14	Separate blinded read protocol	No	No	Yes
15	Data assessed	3 cardiac axes Polar map	3 cardiac axes Polar map	3 cardiac axes Cine planar image
16	Stress/rest paired image read	Yes	Yes	Yes
17	Images randomized for read	Yes	Yes	Yes
18	Monitoring of blinded read	No	No	Yes
19	Blinded reader CRF's	No	No	Yes
20	Separate days for each reader	No	No	Yes
21	Readers are Nuclear Cardiologists	Fellow or attending	Fellow or attending	Attending
22	Criteria for abnormal study	≥1 segment abnl. (apex not used)	≥1 segment abnl. (apex not used)	≥1 segment abnl.
23	Assess intra-reader variability	No	No	Yes
24	Assess inter-reader variability	No	No	Yes
25	Reconstruction filter	Not recorded	Not recorded	Low-pass ramp

(Ref. Tables pp. 3-4, 75-76 of Submission SEI 003 BM)

Case report forms and statistical analysis plans for both protocols were also submitted. In addition, the Sponsor included copies of *Imaging Guidelines for Nuclear Cardiology Procedures* published by the American Society of Nuclear Cardiology (ASNC) (*J. Nuclear Cardiology* March/April 1999. According to the Sponsor, these re-read protocols were designed in accordance with cardiac imaging guidelines in the above ASNC reference as well as guidelines in the draft FDA *Guidance for Industry: Developing Medical Imaging Drugs and Biologics*: section 8b on conduct of blinded reads. The blinded reads for both protocols were conducted at the _____

5:2:1:2 Protocol Design and Description: P53-006

a) Processing of raw image data: Raw image data from the perfusion studies were stored on 8 inch floppy discs and optical storage discs from the individual study sites. All images were transferred to a common format for processing on the _____ Computer System.

_____ One trained Nuclear Cardiology technologist at the core laboratory processed the above data into the three

5:2:2 Results: Report 2954A (Study P53-006)

The evaluation of efficacy in this study addressed the primary endpoints of sensitivity, specificity and predictive values of Myoview SPECT for CAD when compared to coronary angiography as a standard of truth, on a subject level and for the individual coronary arteries.

5:2:2:1 Datasets Analyzed

Fifty-nine subjects were evaluable in the original dataset for Study P53-006, of which 58 were considered interpretable for the original blinded consensus read. Due to technical difficulties, ten image sets were not recoverable, leaving a maximum of 49 evaluable image sets for the new blinded read. Reader 2 also considered 3 additional scans uninterpretable, leaving 46 subjects.

5:2:2:2 Demographics

In the original and new datasets, the criterion for a positive CAD diagnosis remains $\geq 50\%$ stenosis in at least 1 vessel. For the new data, a stenosis of $\geq 70\%$ in the left main (LM) artery was added to the criteria (in keeping with current clinical practice). This did not change the number of subjects diagnosed with CAD with respect to overall diagnosis and number of diseased vessels. LM disease is considered multivessel disease (LAD and LCx). Table #5.3 below indicates the number of evaluable subjects:

Table #5.3: Evaluable Subjects: Number of Diseased Vessels on Angiography P53-006 Report 2954A

Reader	Tracer	# of Subjects Evaluable for Efficacy	Number (%) of Angiographically Diseased Vessels			
			0 n (%)	1 n (%)	2 n (%)	3 n (%)
New Reader 1	Myoview	49	11 (22.5)	18 (36.7)	10 (20.4)	10 (20.4)
New Reader 2	Myoview	46	10 (21.7)	17 (37.0)	10 (21.7)	9 (19.6)
New Reader 3	Myoview	49	11 (22.5)	18 (36.7)	10 (20.4)	10 (20.4)
Consensus Read	Myoview	58	13 (22.4)	21 (36.2)	11 (19.0)	13 (22.4)

(Ref. Modified from Table #11.2, p. 027, vol. 2 of submission)

5:2:2:3 Comparison with Angiography: Subject-based Analysis

Comparisons between coronary angiograms and Myoview scintiscans are presented for each of the 3 blinded readers as well as for the original consensus read; reported as sensitivity, specificity, positive and negative predictive values, kappa statistic and percent exact agreement. The data are presented in Tables #5.4–5.7 on the next page. The tables are derived from Table 11.3.1.1 in the text of the submission, broken down into 4 smaller tables (one for each blinded reader and the original consensus read) for clarity.

TABLES # 5.4 - 5.7: SUBJECT - BASED COMPARISONS: P53-006 Report 2954A

Table #5.4: Subject-Based Comparison of Angiography with SPECT: Blinded Reader 1

Coronary Angiography Data	New Blinded Read: Reader 1: SPECT		
	Normal (n)	Abnormal (n)	Total (n)
Not Diseased	6	5	11
Diseased	7	31	38
Total	13	36	49
Sensitivity (95% Confidence Int.)	81.6% (69.3-93.9%)		
Specificity (95% Confidence Int.)	54.6% (25.1-84.0%)		
Positive predictive value (95% Confidence Int.)	86.1% (74.8-97.4%)		
Negative predictive value (95% Confidence Int.)	46.2% (19.1-73.3%)		
Kappa statistic (95% Confidence Int.)	0.34 (0.04-0.64)		
Percent Exact Agreement (95% Confidence Int.)	75.5% (63.5-87.6%)		

Table #5.5: Subject-Based Comparison of Angiography with SPECT: Blinded Reader 2

Coronary Angiography Data	New Blinded Read: Reader 2: SPECT		
	Normal (n)	Abnormal (n)	Total (n)
Not Diseased	5	5	10
Diseased	6	30	36
Total	11	35	46
Sensitivity (95% Confidence Int.)	83.3% (71.2-95.5%)		
Specificity (95% Confidence Int.)	50.0% (19.0-81.0%)		
Positive predictive value (95% Confidence Int.)	85.7% (74.1-97.3%)		
Negative predictive value (95% Confidence Int.)	45.5% (16.0-74.9%)		
Kappa statistic (95% Confidence Int.)	0.32 (0.01-0.64)		
Percent Exact Agreement (95% Confidence Int.)	76.1% (63.8-88.4%)		

Table #5.6: Subject-Based Comparison of Angiography with SPECT: Blinded Reader 3

Coronary Angiography Data	New Blinded Read: Reader 3: SPECT		
	Normal (n)	Abnormal (n)	Total (n)
Not Diseased	9	2	11
Diseased	20	18	38
Total	29	20	49
Sensitivity (95% Confidence Int.)	47.4% (31.5-63.2%)		
Specificity (95% Confidence Int.)	81.8% (59.0-100%)		
Positive predictive value (95% Confidence Int.)	90.0% (76.9-100%)		
Negative predictive value (95% Confidence Int.)	31.0% (14.2-47.9%)		
Kappa statistic (95% Confidence Int.)	0.19 (-0.01-0.38)		
Percent Exact Agreement (95% Confidence Int.)	55.1% (41.2-69.0%)		

Table #5.7: Subject-Based Comparison of Angiography with SPECT: Consensus Read

Coronary Angiography Data	Original Consensus Read: SPECT		
	Normal (n)	Abnormal (n)	Total (n)
Not Diseased	4	9	13
Diseased	2	43	45
Total	6	52	58
Sensitivity (95% Confidence Int.)	95.6% (89.5-100%)		
Specificity (95% Confidence Int.)	30.8% (5.7-55.9%)		
Positive predictive value (95% Confidence Int.)	82.7% (72.4-93.0%)		
Negative predictive value (95% Confidence Int.)	66.7% (29.0-100%)		
Kappa statistic (95% Confidence Int.)	0.33 (0.03-0.62)		
Percent Exact Agreement (95% Confidence Int.)	81.0% (71.0-91.1%)		

(Ref. Tables # 5.3-5.6 modified from Table #11.3.1.1, p. 028, vol. 2 of submission)

Reviewer's comment: It is quite clear from the tables above that the sensitivities for each blinded reader for detecting CAD using Myoview are lower than for the consensus read. The Sponsor attributes this to the more stringent blinded reading procedures followed the second time around. In the case of Blinded Reader 3, the sensitivity of Myoview was only 47.4%, approximately half that of the consensus read. With regard to the specificity of Myoview for detecting CAD, the results for Blinded Readers 1 and 2 improve by 23.8% and 19.2% over the consensus read, respectively. For Reader 3, the specificity increases 51.0%. Though these may sound like improvements, these changes are associated with corresponding drops in sensitivity and are not in of themselves impressive given the high prevalence of disease (approx. 78% for each of the 3 readers).

5:2:2:4 Comparison with Angiography: Vessel-based Analysis

Comparisons between coronary angiograms and Myoview scintiscans are also presented for each of the major coronary arteries, for each blinded reader as well as for the original consensus read. As in the subject-level analysis, sensitivity, specificity, positive and negative predictive values, kappa statistic and percent exact agreement are given. The data presented on the next 3 pages (Tables #5.8 to 5.19) are derived from Tables 11.3.1.2A-C in the text of the submission, each table in the submission broken down into 4 tables (1 for each new reader plus the original consensus read) for clarity.

Reviewer's comments: Review of the sensitivities for detecting LAD disease (44.4%, 56.0% and 29.6% for Blinded Readers 1, 2 and 3, respectively) indicate values well below that for the consensus read (71.0%). For the LCx, sensitivities for the blinded readers were on a par with those for the consensus read (35.0%; 52.6% and 40.0% for Blinded Readers 1, 2 and 3, respectively, compared to 40.0% for the consensus read). For the RCA, sensitivities for the blinded readers were consistently lower than that for the consensus read (76.2%, 75.0% and 42.9% for Readers 1, 2 and 3, respectively, compared to 96.2% for the consensus read). Specificities were higher for all new readers than for the consensus read in the LAD and RCA, and 2 of the 3 readers in the LCx.

The Sponsor attributes the poor sensitivity values for Myoview (both subject and vessel level) to more stringent blinding protocols, restricting clinical information from the readers. Though this may explain the results in part, the data from the new blinded read are not robust, and results are inferior to those from the consensus read.

(Ref. Tables # 5.8-5.19 modified from Tables #11.3.1.2A-C, pp. 030-033, vol. 2 of submission)

TABLES # 5.8 - 5.11: LAD - BASED COMPARISONS: P53-006 Report 2954A

Table #5.8: Comparison of Angiography with SPECT - LAD: Blinded Reader 1

Coronary Angiography Data	New Blinded Read: Reader 1: SPECT		
	Normal (n)	Abnormal (n)	Total (n)
Not Diseased	19	3	22
Diseased	15	12	27
Total	34	15	39
Sensitivity (95% Confidence Int.)	44.4% (25.7-63.2%)		
Specificity (95% Confidence Int.)	86.4% (72.0-100%)		
Positive predictive value (95% Confidence Int.)	80.0% (59.8-100%)		
Negative predictive value (95% Confidence Int.)	55.9% (39.2-72.6%)		
Kappa statistic (95% Confidence Int.)	0.29 (0.06-0.53)		
Percent Exact Agreement (95% Confidence Int.)	63.3% (49.8-76.8%)		

Table #5.9: Comparison of Angiography with SPECT - LAD: Blinded Reader 2

Coronary Angiography Data	New Blinded Read: Reader 2: SPECT		
	Normal (n)	Abnormal (n)	Total (n)
Not Diseased	15	6	21
Diseased	11	14	25
Total	26	20	45
Sensitivity (95% Confidence Int.)	56.0% (36.5-75.5%)		
Specificity (95% Confidence Int.)	71.4% (52.1-90.8%)		
Positive predictive value (95% Confidence Int.)	70.0% (49.9-90.1%)		
Negative predictive value (95% Confidence Int.)	57.7% (38.7-76.7%)		
Kappa statistic (95% Confidence Int.)	0.27 (0.00-0.54)		
Percent Exact Agreement (95% Confidence Int.)	63.0% (49.1-77.0%)		

Table #5.10: Comparison of Angiography with SPECT - LAD: Blinded Reader 3

Coronary Angiography Data	New Blinded Read: Reader 3: SPECT		
	Normal (n)	Abnormal (n)	Total (n)
Not Diseased	22	0	22
Diseased	19	8	27
Total	41	8	49
Sensitivity (95% Confidence Int.)	29.6% (12.4-46.9%)		
Specificity (95% Confidence Int.)	100% (100-100%)		
Positive predictive value (95% Confidence Int.)	100% (100-100%)		
Negative predictive value (95% Confidence Int.)	53.7% (38.4-68.9%)		
Kappa statistic (95% Confidence Int.)	0.27 (0.10-0.45)		
Percent Exact Agreement (95% Confidence Int.)	61.2% (47.6-74.9%)		

Table #5.11: Comparison of Angiography with SPECT - LAD: Consensus Read

Coronary Angiography Data	Original Consensus Read: SPECT		
	Normal (n)	Abnormal (n)	Total (n)
Not Diseased	12	15	27
Diseased	9	22	31
Total	21	37	58
Sensitivity (95% Confidence Int.)	71.0% (55.0-87.0%)		
Specificity (95% Confidence Int.)	44.4% (25.7-63.2%)		
Positive predictive value (95% Confidence Int.)	59.5% (43.6-75.3%)		
Negative predictive value (95% Confidence Int.)	57.1% (36.0-78.3%)		
Kappa statistic (95% Confidence Int.)	0.16 (-0.09-0.41)		
Percent Exact Agreement (95% Confidence Int.)	58.6% (46.0-71.3%)		

TABLES # 5.12 - 5.15: LCx - BASED COMPARISONS: P53-006 Report 2954A

Table #5.12: Comparison of Angiography with SPECT - LCx: Blinded Reader 1

Coronary Angiography Data	New Blinded Read: Reader 1: SPECT		
	Normal (n)	Abnormal (n)	Total (n)
Not Diseased	26	3	29
Diseased	13	7	20
Total	39	10	49
Sensitivity (95% Confidence Int.)	35.0% (14.1-55.9%)		
Specificity (95% Confidence Int.)	89.7% (78.6-100%)		
Positive predictive value (95% Confidence Int.)	70.0% (41.6-98.4%)		
Negative predictive value (95% Confidence Int.)	66.7% (51.9-81.5%)		
Kappa statistic (95% Confidence Int.)	0.27 (0.01-0.052)		
Percent Exact Agreement (95% Confidence Int.)	67.4% (54.2-80.5%)		

Table #5.13: Comparison of Angiography with SPECT - LCx: Blinded Reader 2

Coronary Angiography Data	New Blinded Read: Reader 2: SPECT		
	Normal (n)	Abnormal (n)	Total (n)
Not Diseased	20	7	27
Diseased	9	10	19
Total	29	17	46
Sensitivity (95% Confidence Int.)	52.6% (30.2-75.1%)		
Specificity (95% Confidence Int.)	74.1% (57.5-90.6%)		
Positive predictive value (95% Confidence Int.)	58.8% (35.4-82.2%)		
Negative predictive value (95% Confidence Int.)	69.0% (52.1-85.8%)		
Kappa statistic (95% Confidence Int.)	0.27 (-0.01-0.55)		
Percent Exact Agreement (95% Confidence Int.)	65.2% (51.5-79%)		

Table #5.14: Comparison of Angiography with SPECT - LCx: Blinded Reader 3

Coronary Angiography Data	New Blinded Read: Reader 3: SPECT		
	Normal (n)	Abnormal (n)	Total (n)
Not Diseased	26	3	29
Diseased	12	8	20
Total	38	11	49
Sensitivity (95% Confidence Int.)	40.0% (18.5-61.5%)		
Specificity (95% Confidence Int.)	89.7% (78.6-100%)		
Positive predictive value (95% Confidence Int.)	72.7% (46.1-99.1%)		
Negative predictive value (95% Confidence Int.)	68.4% (53.6-83.2%)		
Kappa statistic (95% Confidence Int.)	0.32 (0.06-0.57)		
Percent Exact Agreement (95% Confidence Int.)	69.4% (56.5-82.3%)		

Table #5.15: Comparison of Angiography with SPECT - LCx: Consensus Read

Coronary Angiography Data	Original Consensus Read: SPECT		
	Normal (n)	Abnormal (n)	Total (n)
Not Diseased	26	7	33
Diseased	15	10	25
Total	41	17	58
Sensitivity (95% Confidence Int.)	40.0% (20.8-59.2%)		
Specificity (95% Confidence Int.)	78.8% (64.8-92.7%)		
Positive predictive value (95% Confidence Int.)	58.8% (35.4-82.2%)		
Negative predictive value (95% Confidence Int.)	63.4% (48.7-78.2%)		
Kappa statistic (95% Confidence Int.)	0.20 (-0.05-0.44)		
Percent Exact Agreement (95% Confidence Int.)	62.1% (49.6-74.6%)		

TABLES # 5.16 - 5.19: RCA - BASED COMPARISONS: P53-006 Report 2954A

Table #5.16: Comparison of Angiography with SPECT - RCA: Blinded Reader 1

Coronary Angiography Data	New Blinded Read: Reader 1: SPECT		
	Normal (n)	Abnormal (n)	Total (n)
Not Diseased	20	8	28
Diseased	5	16	21
Total	25	24	49
Sensitivity (95% Confidence Int.)	76.2% (58.0-94.4%)		
Specificity (95% Confidence Int.)	71.4% (54.7-88.2%)		
Positive predictive value (95% Confidence Int.)	66.7% (47.8-85.5%)		
Negative predictive value (95% Confidence Int.)	88.0% (64.3-95.7%)		
Kappa statistic (95% Confidence Int.)	0.47 (0.22-0.71)		
Percent Exact Agreement (95% Confidence Int.)	73.5% (61.1-85.8%)		

Table #5.17: Comparison of Angiography with SPECT - RCA: Blinded Reader 2

Coronary Angiography Data	New Blinded Read: Reader 2: SPECT		
	Normal (n)	Abnormal (n)	Total (n)
Not Diseased	13	13	26
Diseased	5	15	20
Total	18	28	46
Sensitivity (95% Confidence Int.)	75.0% (56.0-94.0%)		
Specificity (95% Confidence Int.)	50.0% (30.8-69.2%)		
Positive predictive value (95% Confidence Int.)	53.6% (35.1-72.0%)		
Negative predictive value (95% Confidence Int.)	72.2% (51.5-92.9%)		
Kappa statistic (95% Confidence Int.)	0.24 (-0.02-0.50)		
Percent Exact Agreement (95% Confidence Int.)	60.9% (46.8-75.0%)		

Table #5.18: Comparison of Angiography with SPECT - RCA: Blinded Reader 3

Coronary Angiography Data	New Blinded Read: Reader 3: SPECT		
	Normal (n)	Abnormal (n)	Total (n)
Not Diseased	23	5	28
Diseased	12	9	21
Total	35	14	49
Sensitivity (95% Confidence Int.)	42.9% (21.7-64.0%)		
Specificity (95% Confidence Int.)	82.1% (68.0-96.3%)		
Positive predictive value (95% Confidence Int.)	64.3% (39.2-89.4%)		
Negative predictive value (95% Confidence Int.)	65.7% (50.0-81.4%)		
Kappa statistic (95% Confidence Int.)	0.26 (0.00-0.53)		
Percent Exact Agreement (95% Confidence Int.)	65.3% (52.0-78.6%)		

Table #5.19: Comparison of Angiography with SPECT - RCA: Consensus Read

Coronary Angiography Data	Original Consensus Read: SPECT		
	Normal (n)	Abnormal (n)	Total (n)
Not Diseased	8	24	32
Diseased	1	25	26
Total	9	49	58
Sensitivity (95% Confidence Int.)	96.2% (88.0-100%)		
Specificity (95% Confidence Int.)	25.0% (10.0-40.0%)		
Positive predictive value (95% Confidence Int.)	51.0% (37.0-65.0%)		
Negative predictive value (95% Confidence Int.)	88.9% (68.4-100%)		
Kappa statistic (95% Confidence Int.)	0.20 (0.03-0.36)		
Percent Exact Agreement (95% Confidence Int.)	56.9% (44.2-69.6%)		

5:2:2:5 Left Main Coronary Artery

Two subjects with angiographically proven LM disease were imaged with Myoview. Both had angiographic 3-vessel disease; Subject US1/007 was found to have a defect involving the LAD distribution by only 1 of 3 blinded readers, and LCx by none of the readers. Subject US1/013 was not found to have a defect involving the LAD or LCx distribution by any of the blinded readers. However, an RCA perfusion defect was seen in both patients by all readers except Reader 3 for Subject US1/007. The Sponsor attributes the failure to detect LM (LAD and/or LCx territory) disease in these subjects to the relative, rather than absolute nature of Myoview perfusion defect visualization; this reviewer concurs. Table #5.20 summarizes the subject- and vessel-level findings for these 2 subjects. Data for the table is taken from the subject data listings in Vol. 3, pp. 278-289. For the purpose of this analysis, LM disease is considered to be multi-vessel disease.

Table #5.20: Comparison of Angiography with SPECT - Left Main Artery P53-006 Report 2954A

Report 2954A	Reader	Subject-level	LAD	LCx	RCA
		Myoview	Myoview	Myoview	Myoview
Subject US1/007 LM, 3-vessel on angio	Reader 1	+	-	-	+
	Reader 2	+	+	-	+
	Reader 3	+	-	-	-
	Consensus	+	+	-	+
Subject US1/013 LM, 3-vessel on angio	Reader 1	+	-	-	+
	Reader 2	+	-	-	+
	Reader 3	+	-	-	+
	Consensus	+	+	-	+

(Ref: Derived from Tables 16.2.6.6 and 7, pp. 278-289, vol.3)

+ = Abnormal - = Normal

5:2:2:6 Single-vessel versus Multi-vessel Disease

In general, the percentage of subjects with documented multivessel CAD were found to have a higher percentage of positive Myoview SPECT studies than those with single-vessel pathology. In all cases (single- and multi-vessel disease for each blinded reader) the sensitivity of Myoview scintigraphy with pharmacologic stress was lower than the corresponding sensitivities computed during the original consensus read. The data are summarized in Table #5.21 below.

Table #5.21: Comparison of SPECT with # of Diseased Vessels: All Reads: P53-006 Report 2954A

Coronary Angiography Diagnosis	New Blinded Read - Reader 1			New Blinded Read - Reader 2		
	Normal n (%)	Abnormal n (%)	Total N	Normal n (%)	Abnormal n (%)	Total N
Single-Vessel Disease	4 (22.2)	14 (77.8)	18	5 (29.4)	12 (70.6)	17
Multi-Vessel Disease	3 (15.0)	17 (85.0)	20	1 (5.3)	18 (94.7)	19
Total	7 (18.4)	31 (81.6)	38	6 (16.7)	30 (83.3)	36
Coronary Angiography Diagnosis	New Blinded Read - Reader 3			Original Consensus Read		
	Normal n (%)	Abnormal n (%)	Total N	Normal n (%)	Abnormal n (%)	Total N
Single-Vessel Disease	10 (55.6)	8 (44.4)	18	2 (9.5)	19 (90.5)	21
Multi-Vessel Disease	10 (50.0)	10 (50.0)	20	0 (0.0)	24 (100)	24
Total	20 (52.6)	18 (47.4)	38	2 (4.4)	43 (95.6)	45

(Ref. modified from Table 11.3.1.4A, p. 035, vol. 2 of submission)

For subjects with angiographically confirmed single-vessel disease, the percents correctly diagnosed to have 1 abnormal vessel distribution underperfused on SPECT were 55.6%, 29.4 % and 22.2% for Blinded Readers 1, 2 and 3, respectively. For the original consensus read, the percent was 19.1%. For subjects with multi-vessel disease, the corresponding percentages correctly diagnosed with multiple abnormal vascular distributions were 30.0, 57.9 and 30.0 for Blinded Readers 1, 2 and 3, respectively. For the original read, the percent was 83.3%. In summary, the new blinded read provided a slightly higher sensitivity only for single-vessel disease; otherwise, the original consensus read provided considerably higher sensitivity values.

5:2:2:7 Inter- and Intra-reader Variability

To evaluate the reproducibility of scan interpretation among readers (*inter-reader variability*), the Spearman correlation coefficient was calculated for subject-level readings only (Table #5.22 below). Data were presented in pairs: Reader 1 and 2, 1 and 3, 2 and 3 and each new reader with the original consensus read. The number of images available for this comparison ranged from 45 to 49.

Table #5.22: Spearman's Rank Correlation Coefficient Among Readers: P53-006 Report 2954A₂

n	Correlation	n	Correlation	n	Correlation
Blinded Readers 1 and 2		Blinded Readers 1 and 3		Blinded Readers 2 and 3	
46	0.712 (p = 0.000)	49	0.499 (p = 0.001)	46	0.470 (p = 0.001)
Consensus Read and Reader 1		Consensus Read and Reader 2		Consensus Read and Reader 3	
48	0.620 (p = 0.000)	45	0.661 (p = 0.000)	48	0.319 (p = 0.069)

(Ref. modified from Table 11.3.1.6, p. 039, vol. 2 of submission)

Images for five subjects were randomly chosen to make an assessment of *intra-reader reproducibility*; images were read in random order, but the time interval between reads was not specified. Readings were on a subject and vessel level; among 15 pairs of subject level reads, 2 were discordant and among 45 pairs of vessel-level reads, 9 were discordant. Two of the 9 discordant reads involved 3 segments while 6 of the reads involved 1 segment. Only the first of each pair of reads was used in the final efficacy analysis.

5:2:2:8 Image Quality Assessment

Rest and stress Myoview images were evaluated by the blinded readers as *optimal* or *suboptimal*, however, the criteria for such evaluation were not specified. For Reader 1, 33 of 49 (67%) of Myoview image pairs (rest and stress) were of optimal quality. For Reader 2, 30 of 46 pairs (65.2%) were optimal, and for Reader 3, 38 of 49 (77.6%) pairs were considered optimal. This assessment was correlated to the subject-level agreement of the Myoview images with coronary angiography. As expected, when 1 or more images for a given subject was suboptimal, the percentages of correct diagnoses were lower (36% to 69%) than when both tests were optimal (61% to 89%). A separate analysis of agreement where both rest and stress exams were suboptimal was not provided, nor was a comparison made with the original consensus read. The inability of a blinded reader to adjust the image (filters, color scales, gray-levels) and render it more interpretable was cited by the Sponsor as a reason for the large number of suboptimal scans.

5:2:2:9 Sponsor's Conclusions: (quoted from Page 044, Vol. 2 of submission)

- "Myoview myocardial perfusion imaging with intravenous dipyridamole pharmacologic stress-testing showed high sensitivity for detection of CAD in this subject population. The slightly lower sensitivity when compared to the original read, is expected given the more stringent blinding procedures [see Table #5.2, page 6 of review] followed during the new blinded reads. The specificities for the detection of CAD for all three independent readers were consistently higher than that observed in the original blinded read. The overall sensitivities for detection of abnormalities in subjects with multi-vessel disease for the new blinded reads were consistent with that observed with the original blinded read".
- "The sensitivity and specificity of Myoview SPECT for the detection of CAD in the LCx for the new blinded read was consistent with that observed for the original blinded reads. The sensitivity for detection of CAD in the LAD and RCA was somewhat lower for the new blinded reads than for the original blinded read. Conversely, specificities were consistently higher for the new blinded reads than for the original blinded read".

5:2:2:10 Reviewer's Conclusions: Study P53-006 Report 2954A

Study design and conduct: Review of this Study Report has demonstrated that the Sponsor has conducted the re-read in a manner consistent with the protocol and the independent blinded read requirement stated in the Approvable Letter of 21 December 1999. The report itself is well organized and the data presented clearly.

Comparison of new independent blinded Myoview read with original consensus read: The sensitivity results for the blinded re-read of Myoview scans in Study P53-006 Report 2954A are lower than those from the original consensus read, on a subject level and vessel level for the LAD and RCA. For the LCx, sensitivity and specificity are on a par with the original consensus read.

Given the "enriched" nature of the study population, one would expect the sensitivity of Myoview to be higher than the results reported here. The Sponsor's explanations for the poor sensitivity of Myoview were more stringent blinding requirements and the fact that blinded interpretation of images may not mimic the clinical situations in which a Myoview study may be used. Though these may explain the results in part, they do not in of themselves answer the need for greater sensitivity on a subject and vessel level.

Image quality: The Sponsor attempted to explain the large number of suboptimal scans as due to the inability of blinded readers to adjust images and render them more interpretable. The scans themselves may also have been of lesser quality, due to out-moded equipment and possible deterioration during archival. An analysis comparing scan quality obtained with the earlier consensus read with the quality seen now was not provided in the submission.

Overall conclusion: This reviewer considers the data presented from the interpretation of images from Study P53-006 by independent blinded readers not sufficient to support the limited indication for Myoview with pharmacologic stress proposed in this resubmission. Even if the data were more robust, a claim for *delineating myocardial ischemia*, as proposed in the labeling, would not be adequately supported by a high sensitivity of Myoview for *detection of CAD*.

5:2:3 Results: Report 2955A (Study PR95-302)

Presented is the evaluation of sensitivity, specificity and predictive values for Myoview and thallium-201 SPECT when compared to coronary angiography as a standard of truth, overall and for the individual vessels, in 26 subjects. As in Report 2954A for Study P53-006, the new blinded reads are compared to the original consensus read.

5:2:3:1 Datasets Analyzed

Twenty-six subjects were evaluable in the original dataset for Study PR95-301, of whom all received Myoview at rest and both Myoview and Tl-201 following dipyridamole stress. Of 26 Myoview scans, 25 were considered interpretable for the original blinded consensus read; all of 26 Tl-201 scans were interpretable. Due to technical difficulties, four image sets were not recoverable for the new blinded readers. For *Blinded Reader 1*, 19 Myoview and 20 Tl-201 image sets were interpretable; for *Blinded Reader 2*, 20 Myoview and 23 Tl-201 sets were interpretable; and for *Blinded Reader 3*, 21 Myoview and 23 Tl-201 sets were readable.

5:2:3:2 Demographics

In the original and new datasets, the criterion for a positive CAD diagnosis remains $\geq 50\%$ in at least 1 vessel. As in Report 2954A for Study P53-006, a stenosis of $\geq 70\%$ in the left main (LM) artery was added to the criteria for CAD (in keeping with current clinical practice). This did not change the number of subjects diagnosed with CAD with respect to number of diseased vessels. All subjects had at least 1 diseased vessel (unlike Study P53-006). Table #5.23 indicates the number of evaluable subjects and vessels.

Table #5.23: Evaluable Subjects: Number of Diseased Vessels PR95-302 Report 2955A

Reader	Tracer	# of Subjects Evaluable for Efficacy	Number (%) of Angiographically Diseased Vessels		
			1 n (%)	2 n (%)	3 n (%)
New Reader 1	Myoview	19	3 (15.8%)	5 (26.3%)	11 (59.0%)
	Tl-201	20	4 (20.0%)	5 (25.0%)	11 (55.0%)
New Reader 2	Myoview	20	3 (15.0%)	5 (25.0%)	12 (60.0%)
	Tl-201	23	4 (17.4%)	6 (26.0%)	13 (56.6%)
New Reader 3	Myoview	21	3 (14.3%)	6 (28.6%)	12 (57.0%)
	Tl-201	23	4 (17.4%)	6 (26.0%)	13 (56.5%)
Consensus Read	Myoview	25	3 (12.0%)	7 (28.0%)	15 (60.0%)
	Tl-201	26	4 (15.4%)	7 (27.0%)	15 (57.7%)

(Ref. modified from Table #11.2, p. 029, vol. 6 of submission)

5:2:3:3 Comparison with Angiography: Subject-based Analysis

Sensitivities of Myoview and Tl-201 were calculated for each new blinded reader as well as the original consensus read. Without subjects free of CAD, specificity could not be computed. Table #5:24 compares sensitivities for Tl-201 and Myoview for each blinded reader and the original read. The table does not include studies considered non-diagnostic by either new readers or at the time of the original consensus read. (See Section 5.2.3.8, page 24 of this review for assessment of image quality). Table #5:25 indicates the proportion of CAD patients correctly diagnosed with single- or multi-vessel disease using Tl-201 or Myoview.

TABLES # 5.24 - 5.25: SUBJECT - BASED COMPARISONS: PR95-302 Report 2955A

Table #5.24: Subject - Based Sensitivity: Myoview and Thallium-201 SPECT

	New Reader 1	New Reader 2	New Reader 3	Consensus read
MYOVIEV	n = 19	n = 20	n = 21	n = 25
n, Sensitivity (95% Confidence Interval)	73.7% (48.8-90.9)	70.0% (45.7-88.1)	76.2% (52.8-91.8)	96.0% (79.7-99.9)
THALLIUM-201	n = 20	n = 23	n = 23	n = 26
n, Sensitivity (95% Confidence Interval)	85.0% (62.1-96.8)	78.3% (56.3-92.5)	87.0% (66.4-97.2)	96.2% (80.4-99.9)

(Ref. derived from Tables #11.3.1.1A and B, p. 031, vol. 6 of submission)

Table #5.25: Subject - Based Correct Diagnoses: Myoview and Thallium-201 SPECT

	New Reader 1	New Reader 2	New Reader 3	Consensus read
MYOVIEV	N=3	N=3	N=3	N=3
N, % subjects w. correct dx. of <u>single</u> -vessel CAD (95% Confidence Interval)	33.3% (0.8-90.6)	33.3% (0.8-90.6)	0% (0-70.8)	66.7% (9.4-99.2)
N, % subjects w. correct dx. of <u>multi</u> -vessel CAD (95% Confidence Interval)	N=16 50.0% (24.7-75.4)	N=17 41.2% (18.4-67.1)	N=18 61.1% (35.8-82.7)	N=20 35.0% (15.4-59.2)
THALLIUM-201	N=4	N=4	N=4	N=4
N, % subjects w. correct dx. of <u>single</u> -vessel CAD (95% Confidence Interval)	0% (0-60.2)	0% (0-60.2)	0% (0-60.2)	50.0% (6.8-93.2)
N, % subjects w. correct dx. of <u>multi</u> -vessel CAD (95% Confidence Interval)	N=16 8.8% (41.3-89.0)	N=19 73.7% (48.8-90.9)	N=19 73.7% (48.8-90.9)	N=22 54.6% (32.2-75.6)

(Ref. derived from Table #11.3.1.1D, p. 033, vol. 6 of submission)

Reviewer's comments: It is clear that subject-based sensitivity for CAD is lower for Myoview than for Tl-201 for all three independent readers, but equivalent to Tl-201 for the consensus read. For the single-vessel CAD patients, the numbers are extremely small (3 and 4). For multi-vessel CAD patients, the % correct diagnoses are consistently lower for Myoview than for Tl-201, for the original consensus read and all three of the new independent readers. The % correct diagnoses are higher, however, when the new reads are compared to the original for both imaging agents.

For the new blinded read, scores were recorded for *total number of abnormal segments in a given image* (extent score), *sum of the severity scores for each segment* (sum defect score) and *sum defect score divided by extent score* (mean defect score). Since the number of segments and scoring system in the new read were different from the original read, comparison of scores between the old and new reads was difficult. However, the scores for Tl-201 and Myoview were compared for each blinded reader and for the original read; no significant differences were seen between Tl-201 and Myoview for any of the 3 scores for any of the 3 new readers. For the original read there was a significant difference between the tracers in the sum defect score only (p=0.031).

5:2:3:4 Comparison with Angiography: Vessel-based Analyses

Comparisons between coronary angiograms and Myoview / Thallium-201 images are also presented for each of the major coronary arteries, for each blinded reader as well as the original consensus read. As in the subject-level analysis, sensitivity, specificity, positive and negative predictive values, kappa statistic and percent exact agreement are given. The data presented on the following pages (Tables #5.26 to 5.37) are derived from Tables 11.3.1.2A,B,D,E,G and H, pp. 037-040, vol. 6 of the submission, broken down by

reader for clarity. Thallium and Myoview results for each reader and vessel are placed side-by-side for easy comparison. For the purpose of this analysis, LM disease (stenosis of $\geq 70\%$) is to be considered multi-vessel disease. Unlike the subject-based analysis, (all patients were positive for CAD), computation of specificity was possible on a vessel-based analysis (some vessels were negative for CAD).

(Ref. Tables #5.26-5.37 modified from Tables #11.3.1.2A, B, D, E, G, H: pp. 037-041, vol. 6 of submission)

TABLES # 5.26 - 5.29: LAD - BASED COMPARISONS: PR95-302 Report 2955A

Table #5.26: Comparison of Angiography with SPECT - LAD: Blinded Reader 1

Coronary Angiography Data	Blinded Reader 1: Myoview	Blinded Reader 1: Thallium-201
Sensitivity (95% Confidence Int.)	40.0% (16.3-67.7%)	66.7% (38.4-88.2%)
Specificity (95% Confidence Int.)	100% (39.8-100.0%)	80.0% (28.4-99.5%)
Positive predictive value (95% Confidence Int.)	100% (54.1-100.0%)	90.9% (58.7-99.8%)
Negative predictive value (95% Confidence Int.)	30.8% (9.1-61.4%)	44.4% (13.7-78.8%)
Percent Exact Agreement (95% Confidence Int.)	52.6% (28.9-75.6%)	70.0% (45.7-88.1%)

Table #5.27: Comparison of Angiography with SPECT - LAD: Blinded Reader 2

Coronary Angiography Data	Blinded Reader 2: Myoview	Blinded Reader 2: Thallium-201
Sensitivity (95% Confidence Int.)	31.3% (11.0-58.7%)	47.1% (23.0-73.2%)
Specificity (95% Confidence Int.)	100% (39.8-100.0%)	83.3% (35.9-99.6%)
Positive predictive value (95% Confidence Int.)	100% (47.8-100.0%)	88.9% (51.8-99.7%)
Negative predictive value (95% Confidence Int.)	26.7% (7.8-55.1%)	35.7% (12.8-64.9%)
Percent Exact Agreement (95% Confidence Int.)	45.0% (23.1-68.5%)	56.5% (34.5-76.8%)

Table #5.28: Comparison of Angiography with SPECT - LAD: Blinded Reader 3

Coronary Angiography Data	Blinded Reader 3: Myoview	Blinded Reader 3: Thallium-201
Sensitivity (95% Confidence Int.)	52.9% (27.8-77.0%)	58.8% (32.9-81.6%)
Specificity (95% Confidence Int.)	100% (39.8-100.0%)	50.0% (11.8-88.2%)
Positive predictive value (95% Confidence Int.)	100% (66.4-100.0%)	76.9% (46.2-95.0%)
Negative predictive value (95% Confidence Int.)	33.3% (9.9-65.1%)	30.0% (6.7-65.3%)
Percent Exact Agreement (95% Confidence Int.)	61.9% (38.4-81.9%)	56.5% (34.5-76.8%)

Table #5.29: Comparison of Angiography with SPECT - LAD: Consensus Read

Coronary Angiography Data	Original Consensus Read: Myoview	Original Consensus Read: Thallium-201
Sensitivity (95% Confidence Int.)	35.0% (15.4-59.2%)	50.0% (27.2-72.8%)
Specificity (95% Confidence Int.)	100% (47.8-100.0%)	50.0% (11.8-88.2%)
Positive predictive value (95% Confidence Int.)	100% (59.0-100.0%)	76.9% (46.2-95.0%)
Negative predictive value (95% Confidence Int.)	27.8% (9.7-53.5%)	23.1% (5.0-53.8%)
Percent Exact Agreement (95% Confidence Int.)	48.0% (27.8-68.7%)	56.5% (34.5-76.8%)

Reviewer's comment: Side-by-side comparisons above clearly show inferior vessel-based sensitivity for Myoview compared to Tl-201 in the LAD across all readers (esp. Reader 1 and 2), as well as the consensus read. Interestingly, the Myoview sensitivities for New Readers 1 and 3 were improved over those for the original consensus read.

TABLES # 5.30 - 5.33: LCx - BASED COMPARISONS: PR95-302 Report 2955A

Table #5.30: Comparison of Angiography with SPECT - LCx: Blinded Reader 1

Coronary Angiography Data	Blinded Reader 1: Myoview	Blinded Reader 1: Thallium-201
Sensitivity (95% Confidence Int.)	33.3% (11.8--61.6%)	47.1% (23.0-72.2%)
Specificity (95% Confidence Int.)	100% (39.8-100.0%)	100% (29.2-100.0%)
Positive predictive value (95% Confidence Int.)	100% (47.8-100.0%)	100% (63.1-100.0%)
Negative predictive value (95% Confidence Int.)	28.6% (8.4-58.1%)	25.0% (5.5-57.2%)
Percent Exact Agreement (95% Confidence Int.)	47.4% (24.5-71.1%)	55.0% (31.5-76.9%)

Table #5.31: Comparison of Angiography with SPECT - LCx: Blinded Reader 2

Coronary Angiography Data	Blinded Reader 2: Myoview	Blinded Reader 2: Thallium-201
Sensitivity (95% Confidence Int.)	43.8% (19.8-70.1%)	57.9% (33.5-79.8%)
Specificity (95% Confidence Int.)	100% (39.8-100.0%)	75.0% (19.4-99.4%)
Positive predictive value (95% Confidence Int.)	100% (59.0-100.0%)	91.7% (61.5-99.8%)
Negative predictive value (95% Confidence Int.)	30.8% (9.1-61.4%)	27.3% (6.0-61.0%)
Percent Exact Agreement (95% Confidence Int.)	55.0% (31.5-76.9%)	60.9% (38.5-80.3%)

Table #5.32: Comparison of Angiography with SPECT - LCx: Blinded Reader 3

Coronary Angiography Data	Blinded Reader 3: Myoview	Blinded Reader 3: Thallium-201
Sensitivity (95% Confidence Int.)	41.2% (18.4-67.1%)	52.6% (28.9-75.6%)
Specificity (95% Confidence Int.)	100% (39.8-100.0%)	100% (39.8-100.0%)
Positive predictive value (95% Confidence Int.)	100% (59.0-100.0%)	100% (69.2-100.0%)
Negative predictive value (95% Confidence Int.)	28.6% (8.4-58.1%)	30.8% (9.1-61.4%)
Percent Exact Agreement (95% Confidence Int.)	52.4% (29.8-74.3%)	60.9% (38.5-80.3%)

Table #5.33: Comparison of Angiography with SPECT - LCx: Consensus Read

Coronary Angiography Data	Original Consensus Read: Myoview	Original Consensus Read: Thallium-201
Sensitivity (95% Confidence Int.)	19.1% (5.5-41.9%)	13.6% (36.5-75.5%)
Specificity (95% Confidence Int.)	100% (39.8-100.0%)	100% (39.8-100.0%)
Positive predictive value (95% Confidence Int.)	100% (39.8-100.0%)	100% (29.2-100.0%)
Negative predictive value (95% Confidence Int.)	19.1% (5.5-41.9%)	17.4% (5.0-38.8%)
Percent Exact Agreement (95% Confidence Int.)	32.0% (15.0-53.5%)	26.9% (11.6-47.8%)

Reviewer's comment: For the LCx, the side-by-side comparisons above show consistently lower vessel-based sensitivities for Myoview compared to Tl-201 across all new readers. For the consensus read Myoview was superior to Tl-201, but 19.1% is low to begin with. The Myoview sensitivities for all of the new readers were improved over those reported for the original consensus read (in contrast to the subject-level results).

TABLES # 5.34 - 5.37: RCA - BASED COMPARISONS: PR95-302 Report 2955A

Table #5.34 Comparison of Angiography with SPECT - RCA: Blinded Reader 1

Coronary Angiography Data	Blinded Reader 1: Myoview	Blinded Reader 1: Thallium-201
Sensitivity (95% Confidence Int.)	71.4% (41.9-91.6%)	80.0% (51.9-95.7%)
Specificity (95% Confidence Int.)	60.0% (14.7-94.7%)	40.0% (5.3-85.3%)
Positive predictive value (95% Confidence Int.)	83.3% (51.6-97.9%)	80.0% (51.9-95.7%)
Negative predictive value (95% Confidence Int.)	42.9% (9.9-81.6%)	40.0% (5.3-85.3%)
Percent Exact Agreement (95% Confidence Int.)	68.4% (43.5-87.4%)	70.0% (45.7-88.1%)

Table #5.35: Comparison of Angiography with SPECT - RCA: Blinded Reader 2

Coronary Angiography Data	Blinded Reader 2: Myoview	Blinded Reader 2: Thallium-201
Sensitivity (95% Confidence Int.)	53.3% (26.6-78.7%)	76.5% (50.1-93.2%)
Specificity (95% Confidence Int.)	60.0% (11.8-88.2%)	50.0% (11.8-88.2%)
Positive predictive value (95% Confidence Int.)	80.0% (44.4-97.5%)	81.3% (54.4-96.0%)
Negative predictive value (95% Confidence Int.)	30.0% (6.7-65.3%)	42.9% (9.98-81.6%)
Percent Exact Agreement (95% Confidence Int.)	55.0% (31.5-76.9%)	69.6% (47.1-86.8%)

Table #5.36: Comparison of Angiography with SPECT - RCA: Blinded Reader 3

Coronary Angiography Data	Blinded Reader 3: Myoview	Blinded Reader 3: Thallium-201
Sensitivity (95% Confidence Int.)	66.7% (38.4-88.2%)	88.2% (63.6-98.5%)
Specificity (95% Confidence Int.)	33.3% (4.3-77.7%)	50.0% (11.8-88.2%)
Positive predictive value (95% Confidence Int.)	71.4% (41.9-91.6%)	83.3% (58.6-96.4%)
Negative predictive value (95% Confidence Int.)	28.6% (3.7-71.0%)	60.0% (14.7-94.7%)
Percent Exact Agreement (95% Confidence Int.)	57.1% (34.0-78.2%)	78.3% (56.3-92.5%)

Table #5.37: Comparison of Angiography with SPECT - RCA: Consensus Read

Coronary Angiography Data	Original Consensus Read: Myoview	Original Consensus Read: Thallium-201
Sensitivity (95% Confidence Int.)	94.4% (72.9-99.9%)	94.7% (74.0-99.9%)
Specificity (95% Confidence Int.)	20.0% (0.5-71.6%)	0.0% (0.0-41.0%)
Positive predictive value (95% Confidence Int.)	81.0% (58.1-94.6%)	72.0% (50.6-87.9%)
Negative predictive value (95% Confidence Int.)	50.0% (1.3-98.7%)	0.0% (0.0-97.5%)
Percent Exact Agreement (95% Confidence Int.)	78.3% (56.3-92.5%)	69.2% (48.2-85.7%)

Reviewer's comment: For the RCA, the side-by-side comparisons above show consistently lower vessel-based sensitivities for Myoview compared to Tl-201 across all new readers. For the original consensus read Myoview and Tl-201 were nearly identical at a very high level (94-95%). Specificity in this vessel was expectedly low. Like the subject-level analysis, and unlike the LAD and LCx, Myoview sensitivities for all of the new readers were worse than those reported for the consensus read.

5:2:3:5 Left Main Coronary Artery

Four subjects (#004, 007, 011 and 024) with angiographically proven LM disease were imaged with both Myoview and Tl-201. Three of the 4 had angiographic 3-vessel disease in addition to the LAD lesion; Subject 024 had LM and RCA disease only; no lesions were present in the LAD or LCx. All disease in this subject was missed by the new readers of the Myoview images. Myoview scans were recoverable for all 4 subjects; Tl-201 was not recoverable from Subject #011. Table #5.38 summarizes the subject- and vessel-level findings for these 4 subjects. Data is taken from the subject data listings in Vol. 7, pp. 271-286. LM disease is considered to be multi-vessel disease.

Table #5.38: Comparison of Angiography with SPECT - Left Main Artery PR95-302 Report 2955A

Report 2955A	Reader	Subject-level		LAD		LCx		RCA	
		Myo.	TI-201	Myo.	TI-201	Myo.	TI-201	Myo.	TI-201
Subject 004 LM, 3-vessel on angio	Reader 1	+	N	-	N	+	N	+	N
	Reader 2	+	+	-	+	+	+	+	+
	Reader 3	+	+	+	-	+	+	+	+
	Consensus	+	+	-	+	+	+	+	+
Subject 007 LM, 3-vessel on angio	Reader 1	+	+	+	+	-	-	+	+
	Reader 2	+	+	+	+	-	-	+	+
	Reader 3	+	+	+	+	-	-	+	+
	Consensus	+	+	+	+	-	-	+	+
Subject 011 LM, 3-vessel on angio	Reader 1	+	0	+	0	+	0	+	0
	Reader 2	+	0	+	0	+	0	+	0
	Reader 3	+	0	-	0	+	0	+	0
	Consensus	+	+	-	-	-	-	+	+
Subject 024 LM, RCA on angio	Reader 1	-	N	-	N	-	N	-	N
	Reader 2	-	+	-	+	-	-	-	+
	Reader 3	-	+	-	+	-	-	-	+
	Consensus	+	+	-	+	-	-	+	+

(Ref: Tables 16.2.6A.6 and 7, pp. 271-286, vol. 7 of submission) + = Abnormal - = Normal
N = Non-diagnostic 0 = Not available

5:2:3:6 Reversibility

As discussed in the Protocol for Blinded Re-read (Section 5:2:1:3 Protocol Design and Description: PR95-302) on page 8 of this review, reversibility was computed on a segment, vessel and subject level for TI-201 as well as Myoview rest-stress pairs. No "standard of truth" is available, as reversibility is a functional process without an angiographic correlate. In this situation, although angiography is not a truth standard for reversibility, TI-201 offers a basis for comparison. Agreement between TI-201 and Myoview on a subject- and vessel level was reported as % exact agreement and 95% confidence interval (Table 5:39). On a segment level, cross tabulations were made for Myoview and TI-201 combined over all segments (for the 3 blinded readers and consensus read), but % exact agreement and confidence intervals were not computed because segmental observations within a given subject were not independent.

Table #5.39: Subject and Vessel Level Agreement of Reversibility Diagnosis between TI-201 and Myoview: PR95-302 Report 2955A
N, % Exact Agreement, (Confidence Interval)

	Subject	LAD	LCx	RCA
Blinded Reader 1	N=15 66.7% (38.4-88.2)	N=12 58.3% (27.7-84.8)	N=12 66.7% (34.9-90.1)	N=11 45.5% (16.8-76.6)
Blinded Reader 2	N=19 52.6% (28.9-75.6)	N=15 80.0% (51.9-95.7)	N=15 53.3% (26.6-78.7)	N=14 35.7% (12.8-64.9)
Blinded Reader 3	N=19 52.6% (28.9-75.6)	N=15 66.7% (38.4-88.2)	N=15 53.3% (26.6-78.7)	N=14 0.0% (23.0-77.0)
Original Consensus Read	N=25 80.0% (59.3-93.2)	N=20 85.0% (2.1-96.8)	N=21 81.0% (58.1-94.6)	N=18 66.7% (41.0-86.7)

(Ref. derived from Table #11.3.1.5, p. 044, vol. 6 of submission)

Reviewer's comment: Agreement is best between the two tracers with respect to the LAD, worst between the tracers with respect to the RCA. Agreement was better across the 3 vessels for the consensus read (as would be expected) than for independent reads.

5:2:3:7 Inter- and Intra-reader Variability

(Ref. Tables #11.3.1.1F, G, H, pp. 035-036, vol. 6 of submission)

The Spearman's rank correlation coefficient R was calculated for both tracers in the subject-level assessment (normal vs. abnormal) using pairs of new readers (1 and 2, 1 and 3, and 2 and 3) and each reader compared to the original read. Values ranged from _____ for Myoview (a good correlation, unlike the other study) and _____ to _____ for TI-201. When assessments by each new reader was compared to the original read, the correlation coefficients were lower (0.35 to 0.40 for Myoview, -0.083 to 0.546 for TI-201). Within each new blinded reader, McNemar's test was used to test the binary response rates between the two tracers; no significant differences were seen between normal TI-201/abnormal Myoview scans and normal Myoview/abnormal TI-201 results for any reader. For the original read, no discordant pairs were recorded.

5:2:3:8 Image Quality Assessment

Rest and stress Myoview and TI-201 images were evaluated by the blinded readers as *optimal* or *suboptimal*, however, the criteria for such evaluation were not specified. This assessment was correlated to the subject-level agreement of the Myoview images with coronary angiography. For Reader 1, 9 of 19 (47.4%) of Myoview image pairs (rest and stress) were considered to be of optimal quality. For Reader 2, 2 of 20 pairs (10.0%) were optimal, and for Reader 3, 3 of 21 (14.3%) of image pairs were considered optimal. The results for TI-201 were considerably better (55.0%, 30.4% and 56.5%, for Readers 1, 2 and 3, respectively). There was no clear relationship between percent correct diagnoses and image quality, but the numbers are extremely small. A separate analysis of agreement where both rest and stress exams were suboptimal was not provided, nor was a comparison made with the original consensus read.

Reviewer's comment: The Sponsor offers an explanation for the poor quality of most Myoview images: 1) the inability of a blinded reader to adjust the image (filters, color scales, gray-levels) and render it more interpretable, and 2) the presence of a large amount of liver/gallbladder uptake. Nevertheless, the large percentage of suboptimal Myoview scans raises a concern, and may explain in part the poor sensitivity performance of Myoview on both a subject and vessel level.

5:2:3:9 Sponsor's Conclusions: (quoted from Page 005, Vol. 6 of submission)

- "Myoview, when used in conjunction with intravenous dipyridamole pharmacologic stress testing, showed high sensitivity for the detection of CAD (70.0% to 76.2%), similar to that seen with thallium-201 (78.3% to 87.0%), and slightly lower than that obtained by consensus read in the original blinded read (96.0% for Myoview, and 96.2% for thallium-201). The slightly lower sensitivity is expected given the more stringent blinding procedures followed during the new blinded reads".
- "The sensitivity and specificity of both tracers (Myoview and thallium-201 SPECT imaging) for the detection of CAD in the LAD, LCx and RCA for the new blinded read were higher or consistent with that observed for the original blinded reads. There were no statistically significant differences between the tracers with respect to sum defect score of the perfusion abnormality for LAD, LCx and RCA for the new blinded read data".

5:2:3:11 Reviewer's Conclusions: PR95-302 Report 2955A

Study design and conduct: As in Study P53-006 Report #2954A, review of this Study Report has demonstrated that the Sponsor has conducted the re-read in a manner consistent with the protocol and the independent blinded read requirement stated in the Approvable Letter. The report itself is well organized and the data presented clearly.

Small population size: At 25 subjects, the study population is even smaller than that for Study P53-006. Even if the sensitivity of pharmacologic-stress Myoview imaging for detecting CAD were better than TI-201 imaging (which it is not), the data from such a small sample size would offer little support for an efficacy claim. For the individual blinded readers, the sample size is further reduced (See Section 5.2.3.1).

Comparison of Myoview with TI-201: On a subject level, the sensitivity is clearly lower for Myoview than for TI-201 across the 3 blinded readers, though not by a large margin (8.3 to 11.3%). On a vessel level, sensitivity for detecting disease was again consistently lower for Myoview than for TI-201, for all 3 new readers and for all 3 vessels. The margins varied widely across readers (5.9 to 26.7% for the LAD, for example), but were fairly consistent from vessel to vessel. With respect to reversibility of perfusion defects, agreement between TI-201 and Myoview is best with respect for the LAD, worst between the tracers with respect to the RCA. Agreement between the tracers was better across the 3 vessels for the consensus read than for the independent blinded reads.

Comparison of new Myoview read with original consensus read: On a subject level, the sensitivity of Myoview for detecting CAD was lower for all 3 new readers than for the original consensus interpretation (margin of 19.8 to 26.0%). On a vessel level, the sensitivity of Myoview was consistently lower for the new readers than the original in the RCA, but higher in the LCx. In the LAD, sensitivity and specificity are on a par with the original read. One would expect the sensitivity of Myoview to be even higher (both on a subject and vessel level) in this population of subjects all of whom had documented CAD.

Poor scan quality: Despite the Sponsor's explanation of the inability of blinded readers to adjust scans and presence of high liver/gallbladder uptake, the large number of suboptimal studies obtained with Myoview remains a serious problem. For one blinded reader, only 47% of the scan pairs (rest + stress) were optimal, and for two of the readers, less than 15% of the scan pairs were optimal. With all 3 readers, the percentages of optimal Myoview scan pairs were always lower than the percentages of thallium-201 scan pairs. These results are considerably poorer than the scan quality results in P53-006 Study Report 2954A.

Overall conclusion: Given the above findings, this reviewer considers the data presented from the independent blinded re-read of Study PR95-302 not sufficient to support the proposed limited indication for Myoview in the setting of pharmacologic stress. Even if the results were more robust, data indicating the ability of Myoview to *detect ischemia* is needed to support the proposed indication directly, rather than sensitivity and specificity data of Myoview for *detection of CAD* presented here.

5:3 Review of Articles from the Literature

5:3.1 Introduction

In the Approvable Letter of 21 December 1999 (Page 2, paragraph 4), it was stated that a new study of Myoview in patients who were “early candidates” for perfusion imaging (including ones without known CAD) would be needed to support the expanded pharmacologic stress indication sought by the Sponsor. It was also stated that available studies in the literature may be used to provide additional support for use of Myoview in this “all-comers” population as well as the restricted indication sought in the present submission.

To provide the above literature support, the Sponsor has conducted a search in 13 databases covering the last ten years (1990-2000). Only articles written in English (or English abstracts of foreign papers) reporting studies conducted in humans were considered acceptable. Search criteria are listed on page 41 of vol. 14 of the submission; these included Myoview (tetrofosmin) with dipyridamole, adenosine and stress agents not yet approved at FDA (arbutamine and dobutamine). Sixty-two (62) articles were retrieved from 3 of the 13 databases: BIOSIS, Energy Science & Technology, and Medline.

All articles were reviewed by the Sponsor 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 factors (amongst others) increase the possibility of relying on published literature alone to support an indication (page 19 of the *Guidance*):

- Multiple studies by different investigators, each with adequate design and consistent findings across studies
- High level of detail in report, including statistical plans, analytical methods and study endpoints as well as a full accounting of all patients
- Clearly appropriate endpoints, objectively assessed and independent of investigator judgment
- Robust results yielding consistent conclusion of efficacy without need for *post-hoc* analyses or reduced datasets (such as “evaluable” subjects)
- Conduct of studies using groups with properly documented operating procedures and a history of implementing such procedures effectively.

5:3.2 Literature Article Selection

In addition to the essential features listed above from the *Guidance*, additional criteria for a satisfactory supportive article were communicated to the Sponsor in the Approvable Letter and the Industry Meeting of 17 February 2000. To satisfy the requirements for supportive literature, an article would need certain “bottom-line” characteristics (derived from page 2, Industry Meeting Minutes 2/17/00):

- Independent blinded reading of images
- Clear description of a prospective study design with defined endpoints similar to those presented in the original NDA #20,372 for Myoview and exercise stress.
- A statistical analysis plan
- Well-described clinical subject population
- A “standard of truth” against which the imaging modality (and drug) would be compared
- $N \geq 25$ subjects

Two additional criteria were listed by the Sponsor as being “discounted” in the Approvable Letter (though no mention of such “discount” was seen in the Letter by this reviewer):

- No dual-isotope studies (i.e. Tl-201 and Tc-labelled perfusion agent)
- No “atypical” stress techniques (i.e. concurrent exercise and pharmacologic stress)

The Sponsor has stated that these criteria were applied to the retrieved papers and that 31 met the basic criteria for consideration. The breakdown of these 31 articles is as follows:

- 15 articles published since sNDA submission in 1999
- 7 articles from the original Integrated Summary of Efficacy (ISE)
- 3 articles based on company-Sponsored clinical trials
- 6 articles from the original sNDA bibliography but not included in the ISE.

From the 31 articles considered by the Sponsor to meet the basic criteria listed on the previous page, 9 were selected for “in-depth” review by the Sponsor. These are represented in Table #5.40 below, which combines information from Tables #3.1 and #3.2 in volume 14 of the resubmission. Eight articles presented results of subject-level analyses of sensitivity and specificity, while 7 articles presented the analyses on a vessel level.

Table #5.40: Sensitivity/Specificity of Myoview SPECT: Selected Literature Articles

Number	Study	Stress agent	Sensitivity (%) / specificity (%)			
			Subject	LAD	LCx	RCA
1	Adachi 1995	Dipyridamole	-- / --	87 / --	83 / --	96 / --
2	He 1997*	Dipyridamole	85 / 55	46 / 76	83 / 86	89 / 46
3	Cuocolo 1996	Adenosine	84 / 92	91 / 100	88 / 92	-- / --
		Exercise	86 / 85	85 / 100	88 / 92	-- / --
4	Cuocolo 1997	Adenosine	79 / 88	81 / 100	83 / 86	-- / --
5	Barletta, Del Bene 1999*	Dobutamine*	100 / 98	-- / --	-- / --	-- / --
6	Barletta, Gallini 1999*	Dobutamine*	-- / --	70 / 94	75 / 79	78 / 90
7	Elhandy 2000*	Dobutamine*	90 / 55	-- / --	-- / --	-- / --
8	Thorley 1995*	Dobutamine*	95 / 80	50 / 75	88 / 80	60 / 88
		Exercise	88 / 87	78 / 90	87 / 95	90 / 71
9	Takeishi 1998*	ATP*	89 / 86	79 / --	63 / --	83 / --

(Ref. derived from Tables #3.1, 3.2 pp. 9-10, vol. 14 of submission)

Literature report of Sponsor’s clinical trial

* Study uses non-approved stress agent

Article in original SEI 003 submission

5:3.3 Reviewer’s Conclusions:

From the table above, both articles by Barletta and those by Elhandy, Takeishi and Thorley used dobutamine or ATP stress, not yet approved by FDA. The articles by Adachi and both by Cuocolo utilized approved stress agents, but were reported in the original SE 003 and do not provide additional support. This leaves the 1997 paper by He et. al., which reports the consensus read data from the Sponsor’s clinical trial P53-006. Noteworthy is a discrepancy between the original P53-006 Study Report and the He 1997 article with respect to subject- and vessel-level sensitivity and specificity results. (See Table #5.40 above and Tables #5.7, 5.11, 5.15 and 5.19 on pages 11-15 of this review). It is clear from the table above that each of the 9 articles has one or more characteristics which would exclude it from consideration as supportive for the current submission. Even though the sensitivity/specificity results in the table above may appear to be satisfactory, the data cannot be used to support an efficacy claim for Myoview for the reasons mentioned above.

6: Overview of Efficacy:

6:1 Introduction:

A discussion of the efficacy data in this resubmission of NDA 20,732 SEI 003 must be focused on the restricted indication sought for inclusion in the labeling of Myoview with pharmacologic stress. The Sponsor is seeking this interim label to allow for imaging patients who are at high risk for CAD and may not be able to achieve an adequate level of exercise stress. With this in mind, an independent blinded re-read was conducted to address the problem of bias which may result from a consensus reading of images.

It was stated in the Industry Meeting of 17 February 2000 that results from this independent blinded re-read must be more robust than those from the original consensus read (especially on a vessel level) to support the restricted labeling. This issue forms the primary focus for evaluating efficacy results from the two blinded re-read reports.

6:2 Reviewer's evaluation of efficacy results:

6:2:1 Report 2954A from Study P53-006 and Report 2955A from Study PR95-302:

Review of the Study Reports has indicated that the Sponsor has conducted the re-reads in a manner consistent with the protocol submitted in March 2000, appropriately responding to clinical and statistical comments sent in May. The reports, and the submission as a whole, are well organized and present the data clearly. It must be emphasized that coronary angiography, the truth standard used here, is an anatomical modality and not an ideal measure of myocardial perfusion (or ischemia / infarction). Nevertheless, the data from both reports has not provided the support necessary to approve the proposed limited indication for Myoview for several reasons, each explained in turn below:

- Sensitivity for CAD less robust for new readers than original consensus read
- Sensitivity for CAD detection lower for Myoview than for Tl-201
- Overall vessel-level sensitivities lower than subject-level sensitivities for both studies
- Subject-level specificity not applicable for PR95-302 Report 2955A (all subjects had CAD)
- Small sample sizes (especially PR95-302 Study Report 2955A)
- Poor scan quality as judged by blinded readers (esp. PR95-302 Study Report 2955A)

Inspection of Table #6.1 below shows a clear drop in subject level sensitivities for Myoview in detecting CAD for both studies. If one discounts the results from Reader 3 for the larger study (whose results were much poorer than the other two), the sensitivity is still consistently (12.3% and 14%) below that for the original read. For the smaller study, the drop in sensitivity is consistent among the readers and more pronounced overall (19.8% to 26%).

Table #6.1: Subject-Based Sensitivity: Myoview SPECT, Study Reports 2954A and 2955A

	New Reader 1	New Reader 2	New Reader 3	Original read
P53-006 STUDY REPORT 2954A	n = 49	n = 46	n = 49	n = 58
n, Sensitivity	81.6%	83.3%	47.4%	95.6%
95% Confidence Interval	(69.3-93.9)	(71.2-95.5)	(52.8-91.8)	(89.5-100)
PR95-302 STUDY REPORT 2955A	n = 19	n = 20	n = 21	n = 25
n, Sensitivity	73.7%	70.0%	76.2%	96.0%
95% Confidence Interval	(48.8-90.9)	(45.7-88.1)	(52.8-91.8)	(79.7-99.9)

(Ref. derived from Tables #11.3.1.1, p. 028, vol. 2 and #11.3.1.1A, p. 031, vol. 6 of submission)

Vessel-level sensitivities of the blinded reads were generally on a par with the consensus read for LCx disease in Study 2954A and LAD disease in Study 2955A, and better than the consensus in the LCx for Study 2955A. Aside from these exceptions, vessel-level sensitivities for the new readers were substantially lower than the consensus read. In

addition, sensitivities for Myoview were lower on a vessel level (for all 3 vessels) than on a subject level, in each of the two studies. Even though improvement was seen with certain readers on a vessel level, Myoview was able to detect perfusion defects in less than half of the territories supplied by stenotic vessels in several instances. The data does not adequately support the ability of Myoview to detect disease on a vessel level, especially in a population where the prevalence of CAD may be lower than in the subject groups studied here.

Comparisons of Myoview with Tl-201 in Study 2955A likewise indicate Myoview to have consistently lower sensitivities than Tl-201 on a subject level (Table #5.24) and on a vessel level (see Tables #5.26-5.37), across the three readers. Thallium, despite its proven efficacy and long-term use, has physical characteristics which prevent it from being an ideal myocardial perfusion agent. These include its long half-life, necessitating a smaller dose (1-3 mCi); and peak energy of 80 KeV, not the optimal energy for current gamma camera systems. The ability of Tl-201 to *redistribute*, however, allows the reader to evaluate both rest and stress images with a single dose, and provides a "dynamic" surrogate for myocardial ischemia and viability. With Tl-201, "reversibility" is indicated by the presence of redistribution. Myoview was developed in an effort to address the physical problems of Tl-201, but lacks the ability to reveal a "dynamic" (i.e. redistributing) image. In this context, "reversibility" for Myoview is simply the difference in uptake scores between static resting and stress Myoview images. An attempt was made by the Sponsor to correlate "reversibility" scores between the two tracers. Agreement was best for the LAD, worst for the RCA. Agreement was better across the 3 vessels for the consensus read (as would be expected) than for independent reads. The Sponsor and this reviewer agree that coronary angiography does not provide a satisfactory truth standard with respect to "reversibility".

Even if sensitivity results discussed above were better on a subject and vessel level, small sample sizes (especially for Study Report 2955A) would still weaken the supportive value of the data. With missing scans for both studies, the numbers are even smaller (as low as 11 subjects for Tl-201-Myoview reversibility comparison, Blinded Reader 1). This reviewer agrees with the Sponsor that a meta-analysis of efficacy data from the two studies would not be appropriate (submission p. 093, vol. 1), given differences in design and study populations.

The issue of image quality raises an even greater concern. As explained above, the physical characteristics of Tc-99m should result in improved image quality over Tl-201, however, the reverse was seen in Study Report 2955A. For 2 readers, less than 15% of Myoview scan pairs (rest + stress) were considered optimal. The Sponsor offers an explanation for the poor quality of most Myoview images: 1) the inability of a blinded reader to adjust the image (filters, color scales, gray-levels) and render it more interpretable, and 2) the presence of a large amount of liver/gallbladder uptake. In addition, the fact that many of the scans were taken from older (pre-1995) studies in the original submission may further contribute to poor quality. Nevertheless, the large percentage of suboptimal Myoview scans raises a concern, and may in part explain the poor sensitivity performance of Myoview on both a subject and vessel level.

6:2:2 Comparison of blinded read data with original exercise Myoview results

In an effort to explain the acceptability of lower sensitivities of Myoview reported for the new blinded readers, the Sponsor has stated that results in the present submission are consistent with those from the pivotal rest/exercise Myoview studies in the original NDA approved in 1996. Review of results from these trials in the current approved labeling indicates Myoview was evaluated on a *percent correct diagnoses* basis, with final clinical diagnosis as the standard of truth. The table in the label is reproduced on the next page as Table #6.2 for both Myoview and Tl-201: