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APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-372/SE1-003

Statistical Review(s)

STATISTICAL REVIEW AND EVALUATION

NDA# 20372 Supplemental Application SE1-003 –A2

Sponsor: Nycomed-Amersham (Medi-Physics)

Drug: Myoview (Tc99m Tetrofosmin for Injection)

Indication: Imaging of the Myocardium

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Medical Officer: Nelson Arnstein, M.D.

Statistical Reviewer: A G Mucci, Ph.D.

Project Manager: Pat Stewart

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Section(0): Overview
Nycomed's earlier NDA#20372 SE1-003 proposed an extension of Myoview's current indication for Exercise Stress SPECT Imaging of the Myocardium to a more inclusive indication for Exercise/ Pharmacologic Stress SPECT Imaging of the Myocardium. The more inclusive indication can, itself, take at least two forms: a restricted indication for patients highly suspect for disease, or an indication for a less restrictive population. NDA #20372 SE1-003 consisted of two small sample clinical trials and several proposed supporting literature studies. Both trials included Angiography as a Standard of Truth. Both trials focused on Sensitivities and Specificities of Myoview with respect to Angiography; the smaller of these trials included Thallium as a comparator. The FDA review of NDA#20372 SE1-003 concluded that this submission was inadequate for several reasons, prominent among which was (1): the use of consensus reads rather than independent blinded reads of the SPECT Images, and (2): the enriched nature of the patient sample which was not representative of the population likely to undergo pharmacologic Stress/Rest SPECT Imaging. The FDA Approvable letter stipulated that a necessary (but not complete) condition for Approval would be a blinded re-read of the data, and that the principal statistics – Sensitivity and Specificity - for this re-read would have to be more "robust" than the consensus statistics. The FDA also requested completion of a new trial which would include a more representative population of patients likely to undergo pharmacologic Stress/Rest SPECT Myocardial imaging. The Sponsor has partially complied with the FDA Approvable Letter stipulations by providing independent blinded re-reads of the original data (Supplement to NDA#20372 SE1-003-A2). These re-read data, which are analyzed in the review below, can, at best, address the viability of claims for the more restricted indication.

Preliminary Remarks Concerning Efficacy Analyses and Results

Three tables which address in broad outline several critical aspects of the overall efficacy results are presented directly below. The sections which follow the presentation of these tables provide more detailed analyses. All analyses performed in this Review are focused on claims for restricted indications (enriched population)since it is only this population that the current re-read submission investigates.

TABLE(I) and TABLE(II) together present evidence that

(1): The re-reads provide disease detection (Sensitivity, Specificity, Accuracy with respect to Angiography) diagnostic efficacy comparable to the consensus read at the vessel level.

(2): The re-reads provide comparable Sensitivities at the subject level as were obtained in previous clinical trials for which Myoview (or Thallium) was approved . (These previous trials focused on and were evaluated with respect to subject level efficacies.)

TABLE(III) suggests that Agreement levels between Myoview and Thallium on the more refined diagnoses – Normal/Reversible/Fixed - were weaker on the re-reads than they were on the consensus read.

Detailed analyses are presented in the sections below which follow the presentation of these three tables.

TABLE(I) below compares the Consensus read to the Majority re-read of the three blinded re-reads for Sensitivity, Specificity, and Accuracy at a Vessel level (with respect to Angiography. Data from the two trials are combined, and the statistics were calculated on a vessel level, with PR530.006 contributing 147 vessels and PR95-302 contributing 57 vessels. Disease prevalence on the combined vessel level was p = .55. As the table indicates, the new re-reads, on the average, decrease sensitivities, increase specificities, and leave accuracies about the same. Note: (Majority decision = x if at least two independent blind reads = x.) In fact, under the hypothesis of no difference in Consensus vs Majority reads for Sensitivity, Specificity, and Accuracy, respectively, the differences in Sensitivities and Specificities are statistically significant (p values = .005, and <.001 respectively), while the difference in Accuracy is not statistically significant (p value = .13).

TABLE(I)
Vessel Level Comparison of Statistics of Consensus vs Majority Re-Read
Trials PR53.006 and PR95-302 Combined
(# Diseased Vessels = 112 # Normal Vessels = 92 Prevalence = .55)

	Sensitivity	Specificity	Accuracy
Consensus	.61	.53	.57
Majority	.47	.82	.63

TABLE(I) suggests Vessel Level comparability in performance of the re-read with the consensus read, (decreased Sensitivities, increased Specificities, comparable Accuracies) but does not evaluate either of these reads with respect to previously attained Sensitivities and Specificities for approved versions of Myoview (and Thallium) myocardial Imagings. An attempt at such a comparison is provided in TABLE(II) below. There are limitations in this table, namely, it is restricted to the subject level, since no vessel level results are available; furthermore, only Sensitivities are available since too few subjects were normal to allow subject level Specificities to be evaluated.

TABLE(II)
Subject Level Sensitivity Comparisons
Current Re-Read Results vs Previous Myoview and Thallium Results

Results from Exercise Stress Myoview NDA (Approved) (Sample Size =142 Subjects)		Results from Pharmacologic Stress Thallium NDA (Approved) (Sample Size = 1100 Subjects)	Results from Current Re-Read Pharmacologic Stress Myoview NDA (Sample size = 68 Subjec
Myoview	Thallium	Thallium	Myoview
.75	.78	.85	.78

TABLE(III) below compares the Consensus read to each of the blinded re-reads with respect to Vessel level Agreement between Myoview and Thallium in disease type classifications - Normal/Reversible/Fixed. These classifications are more refined than the Defect/No Defect dichotomy required for Sensitivities and Specificities; moreover, Angiography is not a standard for evaluating such distinctions, consequently Thallium serves somewhat as a standard here since it is approved for these distinctions. Only data from the smaller trial, PR95-302 , was used since this study alone provided Thallium SPECT images. 18 patients were included in the analysis, consequently the sample size consisted of 54 vessels.

TABLE(III)
Perfusion Classification Agreement Levels – Myoview vs Thallium
(Vessel Level N = 54)

Reader#1 Myoview vs Thallium	Reader#2 Myoview vs Thallium	Reader#3 Myoview vs Thallium	Consensus Read Myoview vs Thallium
.48 (26/54)	.55 (30/54)	.59 (32/54)	.78 (42/54)

Section(1): *Description of Current and Previous Trials and Proposed Indications*

Nycomed's *NDA#20372 SE1-003* (Myoview for Pharmacologoic Stress/Rest SPECT Imaging of the Myocardium February 1999) presented results from two clinical trials (P95-302 and P53.006) and several literature studies in support of the Sponsor's proposed extension of the current Exercise Stress/Rest Imaging Indication to one or another more inclusive Exercise and/or Pharmacologic Stress/Rest Imaging Indications. The original *Exercise Stress/Rest NDA # 20372* submission from June 1993 was resubmitted as *NDA#20372 Amendment* in August 1995 and approved in January 1996. The approved Exercise Stress/Rest Imaging Indication and two proposed extensions are presented directly below:

Current Approved Indication:
Myoview is indicated for the Scintigraphic Imaging of the Myocardium following separate administrations under Exercise and Resting conditions. It is useful in the *Delineation of regions of reversible Myocardial Ischemia* in the Presence or Absence of Infarcted Myocardium.

Proposed Extended Indication#1(Restricted Population):

Proposed Extended Indication#2 (More Representative Population):

A detailed description of the statistical design and analyses for NDA#20372 SE1-003 can be found in the Statistical Review and Evaluation of this NDA, dated 12-20-99 . A summary of the design is given directly below:

Description of the Study Design of NDA# 20372 SE1-003:

All studies (clinical trials and literature) utilized approved pharmacologic stress agents – dipyridamole for the clinical trials, adenosine for the literature studies. Only one study – Clinical trial PR95-302 provided an approved Comparator , namely Thallium. All studies provided consensus blinded reads of Myoview SPECT Images (and, when available, Thallium Images) which were evaluated for Detection, Localization, and Type of disease, where:

Detection = Presence = Evidence on Image of a Perfusion Defect at Stress or Rest

Localization = Region of Myocardium where Perfusion Defect was found

Type= Infarct if Stress and Rest both register the same level of perfusion defect ; Ischemia if Stress registers a higher perfusion defect level than Rest.

Angiography furnished the Standard of Truth for these studies, and was used for confirmation of presence and localization of disease, but not for confirmation of disease type, since *angiographic readings cannot provide distinctions between Ischemia and Infarct.* Statistical evaluations – Sensitivity/Specificity/Accuracy of Myoview/Thallium diagnoses – involved evaluations of levels of concordance between angiography and the SPECT Images, both on a subject and a vessel level. For disease localization (vessel level) evaluations, the myocardium was partitioned into three regions, each of which was uniquely associated with one of the three arterial vessels: LAD, LCx, RCA. These vessels were classified as diseased/normal accordingly as they presented stenosis/no stenosis on angiography. Concordance between Myoview/Thallium Images and Angiography occurred whenever stenosis/no stenosis in a vessel was reflected as perfusion defects/no perfusion defects in the corresponding myocardial region. Subject level concordance for disease (presence as distinguished from localization of disease) required only that a Myoview diagnosis of a perfusion defect in any of the three myocardial regions was coupled with an angiographic diagnosis of stenosis on any of the three arterial vessels, so that concordance for disease could obtain without correct disease localization. On either the vessel or subject level, the relevant statistics with respect to Angiography are defined per the representative table below:

Representative Table (A)

	A = No Stenosis	A = Stenosis
M = No Perfusion Defect	N_{00} = #True Negatives	N_{01} = #False Negatives
M = Perfusion Defect	N_{10} = #False Positives	N_{11} = #True Positives

Sensitivity = $N_{11}/(N_{01} + N_{11})$

Specificity = $N_{00}/(N_{00} + N_{10})$

Accuracy = $(N_{00} + N_{11})/(N_{00} + N_{11} + N_{01} + N_{10})$

In the small sample clinical trial (PR95-302) in which Thallium Images were obtained, a direct comparison of Myoview to Thallium with respect to diagnoses of disease type was performed. This comparison involved Agreement levels. Agreement can be defined on various levels, depending on Normal/Ischemia/Infarct definitions, which are as follows:

Vessel Level definition of Type:
If a region of the myocardium associated with a vessel presents no perfusion defects, then The region is defined to be Normal; if a region of the myocardium associated with a vessel presents at least one partially or fully reversible perfusion defect, the region is defined to be Ischemic; if a region of the myocardium presents a fixed defect and no reversible defects, then the region is defined as Infarct.

Subject Level definition of Type:
If all three myocardial regions are Normal, the subject is Normal; if at least one myocardial region is Ischemic, the subject is Ischemic; otherwise the subject classification is Infarct.

It is possible to define these classifications on the finer level of myocardial segments since each region is composed of several segments which the case report forms require to be classified as normal/reversible perfusion defect/fixed defect, but, for several reasons elaborated upon at appropriate places below, segment level analyses will not be reported upon.

The table directly below defines Agreement, subject to these definitions.

Representative Table(B)

Myoview/Thallium	Myoview = Normal	Myoview=Ischemia	Myoview=Infarct
Thallium = Normal	N_{00}	N_{01}	N_{02}
Thallium = Ischemia	N_{10}	N_{11}	N_{12}
Thallium = Infarct	N_{20}	N_{21}	N_{22}

Agreement = $(N_{00} + N_{11} + N_{22})/N$ where N = Sum of N_{ij}

Note: Thallium is currently approved for pharmacologic stress evaluations of perfusion of the myocardium. The relevant indication is presented under dipyridamole labeling as follows:

Dipyridamole injection is indicated as an alternative to exercise in Thallium myocardial perfusion imaging for the evaluation of coronary artery disease in patients who cannot exercise adequately.

The labeling then describes the subject level disease detection Sensitivities and Specificities of Thallium (with respect to angiography) which furnished the support for this indication. As previously noted, angiography is inadequate as a Standard of Truth for validation of perfusion defect types – Infarct vs Ischemia. Nonetheless, the indication above has been interpreted in practice to mean that Thallium is reliable for pharmacologic Stress evaluations of fixed versus reversible perfusion defects. Furthermore, the current Exercise Stress indication for Myoview, presented above, explicitly qualifies Myoview as adequate for distinguishing reversible from fixed perfusion defects, although the evidence from the clinical trials supporting this indication, as with the evidence from the clinical trials supporting the pharmacologic Stress Thallium trials, is once more based on defect Sensitivities and Specificities with respect to angiography. These circumstances would suggest that acceptable evidence for the proposed extended indications for disease delineations – reversible vs fixed perfusion for pharmacologic stress Myoview imagings of the myocardium would be Sensitivity/Specificity studies of Myoview with respect to angiography, possibly with Thallium as a comparator, and/or studies which directly compare Myoview with Thallium with respect to Disease Type diagnoses. These avenues leave somewhat underspecified the levels of Sensitivity, Specificity and Myoview/Thallium Agreement which would be considered adequate. The FDA's current position on these statistics will be elaborated upon in the *Problems in the Design* section below.

Section(2):Problems in the Design:
The FDA, in its Approvable Letter, and in a subsequent Industry Meeting with the sponsor, (2-07-00) expressed several concerns regarding the NDA#20372 SE1-003 submission, both the principal FDA concerns regarding the appropriateness of the NDA submission with respect to the proposed extended indications were:

(A): The populations were biased towards patients with known cardiac disease and are therefore not representative of the spectrum of patients likely to undergo pharmacologic stress perfusion imaging. The FDA Approvable letter requested a *new* study of a *more representative* group of patients. The FDA also suggested that if well-designed and sufficiently well reported studies of such representative populations exist in the recent literature, they should be submitted and they would be examined as additional sources of evidence for a Pharmacologic Stress/Rest Imaging Indication.

(B): The blinded reads in all the studies were 'consensus' reads (The readers read the images as a team rather than independently.) Moreover, the readers were familiar with the protocols and were engaged in the image acquisition, and therefore had some knowledge or expectations regarding disease prevalence and the contents of the images prior to the consensus blinded read. The FDA strongly suggested that the images from the two pivotal trials be re-read independently by several new blinded readers who had no

connection with the data acquisition and no knowledge of the protocols. *Moreover, the FDA stipulated during the Industry Meeting (2-17-2000) that the re-reads would have to yield more robust results, on both a subject and vessel level, in order for the proposed restricted labeling (Proposed Extended Indication#1) to be considered.*

(C): The sample sizes in the principal clinical trials were small, and the supporting evidence from literature studies was limited. An examination of the literature studies submitted in support of NDA#20372 SE1-003 revealed that only one such study presented both sufficient detail and similarity in design to the pivotal trials to warrant potential inclusion as additional evidence in support of a pharmacologic Stress/Rest Imaging Indication, namely Cuocolo 1996. This literature study involved 41 patients. The two pivotal trials themselves were similarly limited with respect to sample sizes – PR95-302 included 25 patients; PR53.006 included 58 patients.

Thus, NDA#20372 SE1-003 was effectively a presentation of results from two small sample clinical trials and one supporting Literature study, all with enriched populations, and all with protocol (and prevalence) informed consensus reads rather than with independent blinded reads. As stipulated in the FDA Approvable Letter (12-21-99), and in the Industry Meeting (2-17-00), FDA consideration of the proposed restricted extended indications would, at the very least, require independent blinded re-reads of the clinical trials data, and the results of these re-reads would have to be more "robust" than the original reads.

Sponsor's Response:
The Sponsor has partially addressed the FDA concerns with resubmissions which are the object of the current review, namely Report 2954-A and Report 2955-A which consist essentially of new blinded re-reads of the images from PR53.006 and PR95-302, respectively, along with submissions of recent literature studies.

Comment1: *Indication#1 would be the target indication addressed by these re-reads of the data submitted under NDA#20372 since the populations studied in these re-read trials are exactly the enriched populations previously studied.*

Comment2: *All the literature studies have proven to be, for one reason or another – use of non-approved stress agents, inclusion of studies which are reports on the pivotal trials, consensus reads or undefined reads, absence of truth standards, use of Myoview SPECT Images in conjunction with Echocardiography for diagnoses - unacceptable.*

Thus, the current resubmission will be reviewed strictly with respect to the re-read data from PR53.006 and PR95-302, and these data will be evaluated strictly in accord with the FDA's stipulation that the re-read statistics need to prove more robust than the previous consensus statistics. The primary statistics under consideration will be Sensitivity, Specificity and Accuracy with respect to the standard of Truth of Angiography, on both the subject and vessel levels. However, in the small sample study (PR95-302) which

included Thallium, Myoview and Thallium will also be compared with respect to Agreement Levels for diagnoses of Ischemia and Infarct (per Table(B) above).

Description of the Re-Read Submissions 2954-A and 2955-A

Three blinded readers independently read the Myoview and Thallium Images from PR95-302; three other blinded readers independently read the Myoview Images from PR53.006. The protocols for these new reads were slightly, but not significantly, different from the earlier protocols: Diagnoses of the Main Left Artery were included as a fourth element along with LAD, LCx, and RCA diagnoses in angiographic reads; the Myocardium was partitioned into 17 rather than 13 segments to be more consistent with current practice. Neither modification impacted the previous identifications of myocardial regions with the three vessels LAD, LCx, and RCA. The statistical endpoints remained the same – Disease Detection Sensitivities, Specificities and Accuracies with respect to angiography on both the subject and vessel levels, along with disease type Agreement Levels between Myoview and Thallium whenever such comparisons were possible (PR95-302.) Per FDA request, the Sponsor provided tables of results for these endpoints which included comparisons of the new reads to the previous consensus reads.

Comment(1): *Although the Sponsor emphasizes that the inclusion of the statistics from the previous consensus reads is presented for informational purposes only, the FDA stipulation that the new blinded reads be more "robust" than the old consensus reads would require that comparisons between the statistics generated by the old vs new reads are essential for Efficacy evaluations.*

Comment(2): *The sponsor reported that not all images were "recoverable" for the new reads: 19 of the original 26 sets of Myoview Images were either completely or in large part recoverable for PR95-302; 49 of 58 sets of Myoview Images were recoverable for PR53.006. (The raw data reflects this loss through the absence of data entries for the implicated patients.) The Sponsor's new tables presented the statistics from the original data bases for the consensus reads; the Reviewer preferred, whenever possible, and for purposes of comparison over identical data bases, to present both the consensus and new read statistics only for the recoverable data bases. Moreover, for those sets which were only partially recoverable, in the sense that one or more, but not all of the new blinded reads registered particular images as Non-Diagnosable, the Reviewer included such Images in his analyses by assigning worst-case scenarios for diagnoses vis a vis Angiography. As it turns out, there is no significant difference in the resulting statistics – tables listing Sponsor vs Reviewer values can be found in the Appendix.*

Section(3):Principal Tables and the Reviewer's Comments:

Table(1) and Table(2) present the re-read vs original consensus Sensitivity, Specificity and Accuracy statistics at Subject and Vessel levels for the recoverable data bases from PR95-302 and PR53.006. (See Table(A) above for definitions.) These statistics were calculated from raw data by the Reviewer according to the worst-case procedures outlined above. (The Appendix will provide Sponsor vs Reviewer comparisons; it will be seen that there are no significant differences in the statistics.) Table(3) presents Subject Level Sensitivity comparisons for the current re-read data and data from the approved NDA submission for Exercise Stress SPECT Imaging; this table is included in order that current Sensitivity levels can be compared to previously attained levels. It is a priori conceivable that the re-read statistics improve upon the consensus statistics but do not compare well with previously achieved statistics. This table suggests that, at least at the subject level, that this is not the case. Table(4) presents Vessel Level Myoview vs Thallium Disease Type Agreement Level statistics from PR95-302. (See Table(B) above for definitions.) Table(5) carries the results of Table(4) one step further by listing mean Agreement levels for the three categories: Myoview vs Myoview, Thallium vs Thallium, Myoview vs Thallium. In effect, just as Table(3) provides earlier statistics against which current Sensitivities can be at least partially assessed, Table(5) provides statistics on various types of Agreement against which Myoview vs Thallium can be at least partially assessed. The contents of Table(5) will be described in detail below.

Table (1)
Reviewer's Statistics For PR53.006 Reads
Myoview Efficacy Statistics with Respect to Angiography

READ	SUBJECT LEVEL (N = 49)			VESSEL LEVEL (N=147)		
	SENS	SPEC	ACC	SENS	SPEC	ACC
Consensus	.97 (.92, 1.0)	.36 (.12,.60)	.84 (.75, .93)	.69 (.60, .78)	.51 (.42, .60)	.59 (.52, .66)
Reader#1	.79 (.68, .90)	.55 (.30, .80)	.73 (.63, .83)	.51 (.41, .61)	.78 (.70, .86)	.66 (.60, .72)
Reader#2	.82 (.72, .92)	.45 (.20,.70)	.73 (.63, .83)	.56 (.46, .66)	.59 (.50, .68)	.58 (.51, .65)
Reader#3	.50 (.37, .63)	.82 (.63, 1.0)	.57 (.45, .69)	.37 (.27,.47)	.90 (.84, .96)	.65 (.59, .71)
Majority	.74 (.62, .86)	.64 (.40, ,88)	.71 (.60, .82)	.50 (.40, .60)	.81 (.74, .88)	.67 (.61, .73)
Prevalence	.78			.46		

Table (2)
Reviewer's Statistics For PR95-302 Reads
Myoview and Thallium vs Angiography
((,) = 90% Confidence Interval)

READ	SUBJECT LEVEL (N= 19)		VESSEL LEVEL (N = 57)					
	Sens Myoview	Sens Thallium	Sens Myoview	Sens Thallium	Spec Myoview	Spec Thallium	Accuracy Myoview	Accura Thalliu
Consensus	.95 (.89, 1.0)	.95 (.89, 1.0)	.48 (.38, .58)	.52 (.42, .62)	.69 (.53, .85)	.54 (.36, .72)	.53 (.45, .61)	.53 (.45, .6
Reader#1	.68 (.54, .82)	.84 (.73, .95)	.41 (.32, .50)	.52 (.42, .62)	.85 (.72, .98)	.54 (.36, .72)	.51 (.43, .59)	.53 (.45, .6
Reader#2	.68 (.54, .82)	.79 (.67, .91)	.36 (.27, .45)	.57 (.47, .67)	.85 (.72, .98)	.62 (.45, .79)	.47 (.39, .55)	.58 (.50, .6
Reader#3	.74 (.61, .87)	.89 (.80, .98)	.50 (.40, .60)	.66 (.57, .75)	.77 (.62, .92)	.62 (.45, .79)	.56 (.48, .64)	.65 (.57, .7
Majority	.74 (.61, .87)	.84 (.73, .95)	.43 (.33, .53)	.64 (.55, .73)	.85 (.72, .98)	.69 (.53, .85)	.53 (.45, .61)	.65 (.57, .7
Prevalence	1.00		.77					

Table(3)
Subject Level Sensitivity Comparisons
Current vs Previous Studies

Myoview Exercise Stress Sensitivities (N=142)		Re-Read Sensitivities for PR95-302 (N=19)				Re-read Sensitivities fo PR53.006 (N=49)	
Myoview	Thallium	Myoview New Read	Thallium New read	Myoview Consensus	Thallium Consensus	Myoview New Read	Myoview Consensus
.75	.78	.70	.84	.95	.95	.81	.97

Note: Re- Reads are Majority Reads.

Table(4)
Agreement Levels – Myoview vs Thallium
(PR95-302)
(Vessel Level N = 54)

Reader#1 Myoview vs Thallium	Reader#2 Myoview vs Thallium	Reader#3 Myoview vs Thallium	Consensus Read Myoview vs Thallium
.48 (26/54)	.55 (30/54)	.59 (32/54)	.78 (42/54)

The reviewer calculated the table entries as follows: Each patient provided a vessel level read – Normal, Ischemia, Infarct, Non-Diagnosable - for both Myoview and Thallium for each of the three vessels LAD, LCx, RCA. (Thus, the reads per vessel looked like pairs such as: Myoview=Infarct, Thallium=Ischemia, or Myoview=Non-Diagnosable, Thallium=Normal, etc.) If either the Myoview or Thallium Read was Non-Diagnosable for any vessel, the pair of Reads for that vessel was omitted from the data base. Agreement was then defined as follows: Let M(i) = Total number of vessels from among the 54 vessels for which Reader(i)'s Myoview and Thallium reads agreed. Then:

Agreement = M(i)/54

Comment on Table(4): The vessel level agreement is fairly consistent over the new reads (about 55%) and is significantly lower than the agreement from the consensus read (78%). The significance of these figures is unclear. The reviewer includes Table(5) below as a table suggestive of the value that could be attached to these Myoview vs Thallium Agreement levels. Each column presents the average Agreement level over all combinations of the indicated comparisons. Thus, Myoview vs Myoview contributes three comparisons – Reader#1(Myoview) vs Reader#2(Myoview), Reader#1(Myoview) vs Reader#3(Myoview), etc; Myoview vs Thallium contributes six comparisons – Reader#1(Myoview) vs Reader#1(Thallium), Reader#1(Myoview) vs Reader#2(Thallium), etc.

Table(5)
Mean Agreement Levels
(N =54)

Myoview vs Myoview	Thallium vs Thallium	Myoview vs Thallium
Mean =.71 Range = ———	Mean = .70 Range = ———	Mean = .54 Range = ———

Note: This Table suggests there is a lower level of Agreement across modalities (about 54%) than within modalities (about 70%).

Conclusions:

(1):The principal statistics (Sensitivity, Specificity, Accuracy, with respect to disease detection with the standard of truth of angiography) are comparable for the re-read and consensus reads: re-read sensitivities are lower than consensus sensitivities; re-read specificities are higher than consensus specificities; re-read accuracies are essentially the same as consensus accuracies. This comparability of efficacy is achieved on both the subject and vessel levels.

(2): Myoview subject level sensitivies on the re-reads are comparable to subject level sensitivities attained by previously approved Stress type/imaging modalities – Thallium with pharmacologic stress, Myoview with exercise stress. (Subject level sensitivity was the decisive statistic in the evaluation of these earlier studies.)

(3): The currently proposed indications for Myoview with pharmacologic stress claim that Myoview is useful in the delineation of regions of reversible myocardial ischemia. This refined diagnosis is not capable of corroboration by the standard of truth of angiography, which addresses only disease detection (at subject or vessel levels). However, all of the currently approved combinations – Thallium with pharmacologic stress, Myoview with exercise stress, etc – either make this same claim in labeling or are used for such differential diagnoses in practice, despite the fact that the relevant NDA efficacy results are, once more, restricted to evaluations of disease detection with respect to angiography. In effect, in all previous NDA approvals, claims for disease delineation have been honored provided efficacy in disease detection has been established, consequently there is precedent for disease delineation claims based solely on disease detection results.

(4): Given the current acceptability of Thallium as a diagnostic for disease delineation (Normal, Ischemia, Infarct) under pharmacologic stress, another approach to the analysis of Myoview for similar diagnostic claims would consist in Myoview vs Thallium agreement level comparisons for these disease delineations. The NDA provided only very limited data relevant to such comparisons – 18 patients evaluated for disease delineation at the vessel level (54 vessels) by both Myoview and Thallium. The agreement levels for Myoview vs Thallium were about 54% on the average, as compared to Myoview vs Myoview and Thallium vs Thallium agreement levels, which were both about 70%. Thus, the limited evidence that is available does not indicate that Myoview and Thallium agree on disease delineation at levels suggested as typical for Thallium vs Thallium agreement.

(5): In conclusion, the limited evidence from the re-read analyses suggests comparable disease detection efficacy between re-read Myoview and consensus read Myoview; furthermore, re-read Myoview presents disease detection efficacy results comparable to the results attained by approved exercise stress or pharmacologic stress imaging agents. However, evidence for comparability with Thallium in disease delineation is less compelling.

/S/ 11/7/00

A G Mucci, Ph. D.
Statistical Reviewer

Concur

/S/ 11/7/00

Michael Welch, Ph. D.

Cc: Archival NDA#20-372
HFD-160/E Jones/S Loewke/N Arnstein
HFD-160/P Stewart
HFD-160/File Copy

Appendix

Sponsor vs Reviewer Statistics for PR53.006 Reads

	Sensitivity		Specificity		Accuracy	
Vessel Level	Sponsor	Reviewer	Sponsor	Reviewer	Sponsor	Reviewer
Reader#1	.51	.51	.82	.78	.68	.66
Reader#2	.61	.56	.65	.59	.63	.58
Reader#3	.37	.37	.90	.90	.65	.65
Consensus	.70	.69	.50	.51	.59	.59
Subject Level						
Reader#1	.82	.79	.55	.55	.76	.73
Reader#2	.83	.82	.50	.45	.76	.73
Reader#3	.47	.50	.82	.82	.55	.57
Consensus	.96	.97	.31	.36	.81	.84

Sponsor vs Reviewer Statistics for PR95-302 Reads

	Sensitivity		Specificity		Accuracy	
Vessel Level	Sponsor	Reviewer	Sponsor	Reviewer	Sponsor	Reviewer
Reader#1 (M)	.48	.41	.87	.85	.56	.51
Reader#1 (T)	.65*	.52	.73*	.54	.65*	.53
Reader#2 (M)	.42	.36	.87	.85	.52	.47
Reader#2 (T)	.60	.57	.69	.62	.63	.58
Reader#3 (M)	.54	.50	.78	.77	.57	.56
Reader#3 (T)	.67	.66	.67	.62	.65	.65
Consensus (M)	.49	.48	.73	.69	.53	.53
Consensus (T)	.53	.52	.50	.54	.49	.53
Subject Level	Sponsor	Reviewer	NA			
Reader#1 (M)	.74	.68				
Reader#1 (T)	.85	.84				
Reader#2 (M)	.70	.68				
Reader#2 (T)	.78	.79				
Reader#3 (M)	.76	.74				
Reader#3 (T)	.87	.89				
Consensus (M)	.96	.95				
Consensus (T)	.96	.95				

STATISTICAL REVIEW AND EVALUATION

NDA# 20372 Supplemental Application SE1-003

Sponsor: Nycomed-Amersham (Medi-Physics)

Drug: Myoview (Tc99m Tetrofosmin for Injection)

Indication: Imaging of the Myocardium

Document Date: February 26 1999

PDUFA Date: December 26 1999

Medical Officer: Nelson Arnstein, M.D.

Statistical Reviewer: A G Mucci, Ph.D.

Project Manager: Pat Stewart

Contents Of Review

This Review is comprised of five Sections:

Section (I): Synopsis of the Submission and Overall Comments and Conclusions

Section (II) Overview of the Clinical Trials and the Literature Studies

Section (III): Detailed Description of the Clinical Trials

Section (IV): Additional Supporting Tables for Efficacy Analysis

Section (V): Conclusions/Recommendations

Section (I) provides the minimal essential background on the submission, along with the Reviewer's Principal Efficacy Analyses and the tables supporting these analyses, followed by the Reviewer's conclusions. All other sections serve largely as detailed support for this section.

Section (II) places the submission in the context of similar recent submissions. The rationale for this presentation is to clarify the several perspectives from which the connections between proposed labeling and the support for such labeling can be viewed.

Section (III) provides the finer details of the submission.

Section (I):Synopsis of the Submissions and the Statistical Review/Conclusions

The Sponsor submitted material on two small clinical trials, along with recent relevant papers from the scientific literature, as support for the proposed extension of the current Exercise Stress/Rest Indication for Myoview Enhanced SPECT Imagings of the heart to the more inclusive Exercise/Pharmacologic Stress/Rest Indication. The Statistical Reviewer examined the scientific literature and concluded that two among these studies were of sufficient similarity in design to the two clinical trials to warrant some consideration in the statistical analysis. However, only one of these two studies could be included in the body of evidence relevant to the expanded Efficacy claim.

Description of the Study Design:

All studies included in the Reviewer's analyses utilized approved pharmacologic stress agents – dipyridamole for the clinical trials, adenosine for the literature studies. All studies provided blinded (consensus) reads of Myoview Images which were then evaluated with respect to the standard of truth of angiography. Myoview Image reads were primarily classified as diseased/normal accordingly as they presented perfusion defect/no perfusion defect in various coronary areas. Angiography reads were primarily classified as diseased/normal accordingly as they presented stenosis/no stenosis in one or more of three major arterial vessels. For purposes of defining concordance/discordance in diagnoses at a vessel level, the heart was partitioned into three major areas, each of which was paired exclusively with one of these three vessels. Vessel level concordance between Myoview Images and angiography occurred whenever, for any such pairing, disease status coincided for Myoview Image Reads and angiography. Subject level concordance for disease required only that a disease diagnosis anywhere on the Myoview Images was coupled with a disease diagnosis anywhere on angiography, while subject level concordance for health required that neither the images nor the angiograms presented with disease anywhere. A more delineated disease classification – Ischemia versus Infarct – was provided in some of these studies. This distinction, which presents as a difference in level of perfusion defect between stress and rest SPECT Images, is not amenable to verification by angiography, consequently, its truth value is either self-corroborating, or receives support from similar differences observed on approved comparator reads – Pharmacologic Stress/Rest Thallium Reads, or Exercise Stress/Rest Myoview Reads, for instance. The latter comparator is used in one of the clinical trials, the former in one of the literature studies. It should be noted that these comparators are also largely self-corroborating in their capacity to make distinctions between infarct and ischemia.

Comments on the Design:

As indicated above, Myoview SPECT Images can be utilized for the detection of disease (presence of a perfusion defect), localization of disease(specification of the arterial vessel whose stenosis presents in the heart images as a perfusion defect), and delineation of disease (distinctions between damaged but still viable tissue (ischemia) versus necrotic tissue (infarct.))

In clinical practice, if a perfusion defect is found, , and if it is decided that the more reliable standard of angiography should then be utilized, either for disease confirmation alone, or for therapy (angioplasty), the angiography will not be carried out "locally", (one vessel diagnosis), but, rather, all arterial vessels will be examined. Thus:

(a): Myoview SPECT Efficacy in *disease localization* does not appear to have as much practical importance as Myoview SPECT Efficacy in *disease detection*. (There is at least one scenario, however, wherein localization could be practically useful: if angioplasty has been performed in a particular artery, then the success of this therapy could be assessed by the absence of perfusion defects on subsequent Myoview SPECT Imagings of the implicated coronary area.)

(b): On the other hand, *disease delineation* – Ischemia vs Infarct - could have practical implications, in that a Myoview SPECT diagnosis of , say, infarct, might lead a practitioner to regard angiography as useless, when, in fact, an arterial stenosis consistent with treatable ischemia might be present (false negatives of this type are important.)

In light of (a) and (b), the Statistical Reviewer will order endpoints as follows

Primary: *Disease detection* -subject level statistics, especially Sensitivity and Specificity - calculated with respect to the standard of truth of angiography.

Secondary: *Disease Delineation* – Ischemia vs Infarct, - evaluated, wherever possible, through comparison with disease delineation results provided by Exercise Stress/Rest Images or Pharmacologic Stress/Rest Thallium Images.

Tertiary: *Disease Location* – Vessel Level Sensitivities, Specificities, etc.

Principal Results:

The three studies included in the Reviewer's analysis (Two clinical trials, one literature study) provided 124 subjects for the subject level statistics. The principal tables supporting this analysis are:

Table(1)– *Subject Level Myoview SPECT vs Angiography Diagnoses* -displays the disposition of all subjects from these combined clinical and literature studies.

Table(2) provides the statistical measures derived from Table(1).

Table(3) provides comparisons of Myoview vs Thallium for Disease Delineation using Data from pivotal trial – PR95-302. This study used dipyridamole pharmacologic stress. This clinical provided a Myoview vs Thallium comparison for its 25 subjects. This comparison was carried out on a segment level – 13 coronary segments per patient. Each segment was classified into one of the three categories Normal, Ischemia, or Infarct.

Table(4) provides a segment level comparison of Exercise Stress Myoview SPECT vs Pharmacologic Stress Myoview SPECT, using adenosine phamacologic stress on 41 patients. The data comes from the literature study – Cuocolo (1996). There were 22 coronary segments per patient. Each segment was classified into one of the three categories Normal, Ischemia, or Infarct.

Table(5) provides vessel level statistics for the various studies.

** Note: All blinded reads in all studies were consensus reads. Current FDA guidelines recommend independent rather than consensus reads.*

Table(1)
CLINICAL = PR53.006 and PR95-302
LITERATURE = CUOCOLO 1996
Subject Level

ANGIO VS MYOVIEW	CLINICAL			LITERATURE			ALL	
	N	D		N	D		N	D
N	4 (5%)	3 (4%)		1 (2%)	0 (0%)		5 (4%)	3 (2%)
D	9 (11%)	67 (81%)		0 (0%)	40 (98%)		9 (7%)	107 (86%)

N = Normal D=Diseased
#Patients(Clinical) = 83 #Patients(Literature)= 41
Note: Clinical used Dipyridamole Stress; Literature used Adenosine Stress

Table(2)
MYOVIEW VS ANGIOGRAPHY STATISTICAL MEASURES
CLINICAL = PR53.006 and PR95-302
LITERATURE = CUOCOLO 1996
Subject Level

	CLINICAL	LITERATURE	ALL
SENS	96%	100%	97%
SPEC	31%	100%	36%
PPV	88%	100%	92%
NPV	44%	100%	63%
ACC	86%	100%	91%
KAPPA	.36	1.0	.38
PREV	84%	98%	89%

Table(3)
SEGMENTAL AGREEMENT MYOVIEW VS THALLIUM
(25 patients 325 Segments)
PROTOCOL 95-302

TL/MYO	NORMAL	ISCHEMIA	INFARCT
NORMAL	212 (65%)	7 (2%)	5 (1%)
ISCHEMIA	12 (4%)	42 (13%)	20 (6%)
INFARCT	9 (3%)	6 (2%)	12 (4%)

Note: Agreement = 82% Kappa = .61

Table(4)
SEGMENTAL AGREEMENT ADENOSINE STRESS VS EXERCISE STRESS
(41 patients 902 Segments)
CUOCOLO(1996)

ADENOSINE/EXERCISE	NORMAL	ISCHEMIA	INFARCT
NORMAL	548 (61%)	23 (3%)	13 (1%)
ISCHEMIA	26 (3%)	62 (7%)	1 (1%)
NFARCT	8 (1%)	12 (1%)	199 (22%)

Note: Agreement = 90% Kappa= .80

Table(5)
STATISTICS ON THE THREE STUDIES AND THEIR COMBINATION
VESSEL LEVEL

	PR 53.006 (N=58) (V=174)	PR 95-302 (N=25) (V=75)	CUOCOLO (96) (N=41) (V=123)	COMBINED (N=124) (V=372)
SENS	70%	48%	86%	69%
SPEC	50%	71%	85%	64%
PPV	55%	88%	88%	72%
NPV	65%	24%	82%	60%
ACC	59%	53%	85%	67%
KAPPA	.10	.06	.70	.33
PREV	59%	79%	57%	57%

Note: N = # Subjects V= # Vessels

Observations on the Tables:

(1): The population sizes and the subject level statistics revealed in Table(1) and Table(2) are consistent with sample sizes and statistics determined in Myoview trials for Exercise Stress/Rest SPECT Images. (This observation will be justified and expanded upon in Section(II) below.) The subject level Sensitivities are high, while the subject level Specificities are more problematic.

(2): The segment level agreement statistics revealed in Table(3) suggest that Pharmacologic Stress Myoview segment level diagnostics are similar to Pharmacologic Stress Thallium segment level diagnostics. The sample size, however, is too small to allow definitive conclusions. The segment level statistics in Table(4) suggest that Adenosine Stress/Myoview segment level diagnostics are similar to Exercise Stress/Myoview. Again, the sample size is too small to allow definitive conclusions.

Note: *the Kappa values in both Table(3) and Table(4) appear to be very good, but since the reads on individual segments are not independent, the force of this statistic is considerably compromised.*

(3): The Vessel Level statistics in Table(5) reveal that Pharmacologic Stress/Rest Myoview SPECT Images are not especially efficacious, in general, for disease location, although their efficacy for this endpoint does appear to improve when adenosine replaces dipyridamole (Cuocolo Study.)

Conclusions:

Pharmacologic Stress/Rest Myoview SPECT Imagings provide Subject Level Sensitivities comparable to the Sensitivities achieved for Exercise Stress/Rest Myoview SPECT Imagings. Subject level Specificity, however, is rather erratic, typically low, and is based on small samples, and therefore should not be utilized in inferences. Thus, the Images are highly likely to detect disease when it is present, but could, conversely, suggest disease in many patients who present with symptoms of coronary disease but whose arterial vessels are not stenosed.

Pharmacologic Stress/Rest Myoview SPECT Imagings provide coronary area disease delineations (Infarct vs Ischemia) consistent with Exercise Stress/Rest Myoview SPECT Imagings when the pharmacologic stress agent is adenosine. The presentation of similar consistency between pharmacologic and exercise stress Myoview SPECT Image statistics when dipyridamole is the stress agent has yet to be investigated.

Pharmacologic Stress/Rest Myoview SPECT Imagings correctly predict the disease status of arterial vessels (localization) for about two out of every three vessels. The localization of arterial disease is not as clinically significant as the detection of arterial disease, although correct localization could serve as corroboration for the success of angioplasty if, subsequent to such a therapeutic procedure Stress/Rest Myoview SPECT Images provide normal perfusion reads for the coronary area supplied by the treated vessel.

None of the conclusions above should be read as definitive since the submitted supporting studies suffer from sample size and design limitations.

Section (II): Expanded Contextual Overview:

Myoview SPECT Imaging of the heart is intended as a non-invasive diagnostic procedure useful in the assessment of coronary disease. Myoview is currently approved for Exercise Stress/Rest Enhanced SPECT Imaging. The Sponsor proposes to extend the Myoview Indication so as to cover Pharmacologic Stress/Rest Enhanced SPECT Imaging. The logic informing either employment, in somewhat simplified form, runs as follows:

(1): Three major arterial vessels – LAD, LCX, RCA - supply blood to three corresponding coronary areas. Arterial narrowings (stenoses) in any of the three major coronary arteries, uncompensated by the development of alternative avenues of blood supply (collaterals) to the corresponding coronary areas, can compromise coronary function and eventually lead to necrosis. The Standard of truth for arterial stenosis is Coronary Angiography, an invasive procedure.

(2): Appropriate non-invasive imagings of the heart – Myoview Enhanced SPECT Imagings under Exercise Stress/Rest, for instance, - will, with varying degrees of success, signal the likelihood of arterial stenosis through the presentation of perfusion defects, that is, reduced blood flow in some coronary segments relative to other coronary segments. The perfusion defect will typically present more prominently on stress images.

(3): In Stress/Rest Imagings, a perfusion defect on a stress image, coupled with a less prominent perfusion defect at rest, constitutes evidence for Ischemia (compromised, but viable coronary tissue). Equal levels of perfusion defect on stress and rest images are evidence for Infarct (tissue necrosis). In terms of patient management, Ischemia is "treatable", that is, the compromised vascular area, though damaged, is not dead; consequently the damage is potentially reversible through angioplasty or bypass. Infarct, however, is not correctable.

In light of (1), (2), and (3) above, it would appear that non-invasive Stress/Rest Enhanced SPECT Images could address three diagnostic objectives:

(A): Detection of Disease – Detection of arterial stenosis through the presentation of a Stress Perfusion defect in one or several segments in a coronary area.

(B): Localization of Disease – Determination of which among the three major arterial vessels are stenosed through correlation with the coronary areas which reveal perfusion defects.

(C): Delineation of Disease – The further characterization of detected and localized perfusion defects as reversible (ischemic) or irreversible (infarcted).

Note: Although the Detection and Localization of stenosis by Stress/Rest Enhanced SPECT Images can be verified by Angiography, no current standard of truth exists for confirmation of diagnoses of ischemia vs infarct. Of course, if the SPECT Images presented ischemia, and this diagnosis led to angioplasty, and subsequent SPECT Images revealed no ischemia, this image-therapy-image scenario might in itself constitute a standard of truth for the original diagnosis. But, for the moment, the validity of Myoview SPECT reads of ischemia or infarct remain somewhat self-corroborating, except when compared to reads of, say, Thallium SPECT images or Cardiolite SPECT images, which, though approved for such delineation, suffer ultimately from the same self-referential limitation.

All the above comments are intended strictly as possible points of reference with respect to which the contents of the current NDA submission could be assessed. In particular, they are intended as guidelines for the investigation of the extent to which the Sponsor's proposed new indication (see below) finds proper support in the submitted Study Reports of the Clinical Trials and the Literature Studies. The main issue here is:

Claims focused on disease delineation cannot currently be assessed through recourse to universally acceptable standards of truth. Since there appears to be no accepted standard of truth for the delineation of ischemia vs infarct, it will be assumed in all that follows that claims for success in such delineation for Pharmacologic Stress/Rest Myoview Enhanced SPECT will not require validation by so stringent a standard, but, rather, will be evaluated through comparisons of such images, either with the currently approved <u>Exercise</u> Stress/Rest Myoview Enhanced SPECT or Pharmacologic Stress/Rest Thallium Enhanced SPECT.

Also, as regards pharmacologic stress agents, the possiblities are Dipyridamole or Adenosine,, since only dipyridamole and adenosine (and not dobutamine) are currently approved.

On the other hand, Detection and Localization of disease will be evaluated against the standard of truth of angiography. Localization evaluations will be carried out on a "vessel" level, that is, the heart will be divided into three areas, and each of these areas will be associated with one of the three major arterial vessels, so that concordance of diagnosis between each such coronary area and the associated arterial vessel will occur whenever perfusion defects are present in the vascular area simultaneously with stenosis in the associated artery, or whenever both the vascular area and the artery are normal. Detection evaluations, on the other hand, will require only the less stringent concordance criterion that a diagnosis of a perfusion defect anywhere in the heart occur simultaneously with a diagnosis stenosis in any of the major arterial vessels, or that both the diagnosis of all three vascular areas of the heart and the diagnoses of all arterial vessels be normal.

The Current Submission and Related Submissions/Approvals:

The Sponsor proposes to extend the current approved Exercise Stress/Rest Indication for Myoview Imaging of the myocardium to include a Pharmacologic Stress/Rest Indication.

Current Approved Indication:
Myoview is indicated for the Scintigraphic Imaging of the Myocardium following separate administrations under Exercise and Resting conditions. It is useful in the Delineation of regions of Reversible Myocardial Ischemia in the Presence or Absence of Infarcted Myocardium.

Proposed Extended Indication:

Draft

Thus, all claims previously made for Myoview under Exercise Stress/Rest Imagings would now be extended to Pharmacologic Stress/Rest Imagings.

In order to provide a context for the discussion and analysis of current submissions provided in support of this new indication, it will be useful to summarize relevant previous approvable/approved submissions and the consequent approved indications.

Two cases will be summarized:

(A): Original NDA 20372 for Exercise Stress/Rest Myoview Enhanced SPECT – submitted June 1993. This NDA received an Approvable classification, with approval contingent on the Sponsor's submission of the subset data and analyses subsequently provided as

(B): NDA 20372 Amendment for Exercise Stress/Rest Myoview Enhanced SPECT – submitted August 1995.

These summaries will be followed by a summary of the current submission for:

(C): Pharmacologic Stress/Rest Myoview Enhanced SPECT

(A): Relevant Clinical Trials Results for the previous Approvable NDA submission for Exercise Stress /Rest Myoview:

A total of 252 patients with clinical evidence of ischemic heart disease or atypical chest pain were referred for Exercise Stress Imaging and were studied in two comparative clinical trials of Exercise Stress/Rest Planar Imaging of Myoview vs Thallium. The Primary Outcome variable was the Percentage of Correct Diagnoses (Sensitivity) with respect to the Final Clinical Diagnosis of Ischemia or Infarct. The Final Clinical Diagnosis was based on several types of clinical evidence, including an Unblinded Investigator Read of the Thallium Images. Angiography was performed on 181 patients, but the Sponsor's analysis did not implicate angiography as essential in the determination of the Final Clinical Diagnosis. In addition to its role as an element in the Final Clinical Diagnosis, Thallium was also used as a Comparator. However, the comparisons of Planar Image Reads, Myoview vs Thallium, were Blinded (Two independent Readers.) Thus, Thallium Images, when read unblindedly, functioned as components of the final clinical diagnosis, but, when read blindedly, constituted a comparator to Myoview images.. The Trial results are summarized in the table below.

Table (a)
Overall Diagnostic Outcome Original NDA
(Sensitivity percentages vis a vis the indicated disease categories)

	THALLIUM		MYOVIEW	
ISCHEMIA	Reader#1	Reader#2	Reader#1	Reader#2
Study 1	78%	75%	66%	64%
Study 2	76%	69%	66%	66%
INFARCT				
Study 1	76%	75%	76%	75%
Study 2	71%	70%	73%	68%

(B): Relevant Clinical Trials Results for the subsequent Approved NDA Amendment

The FDA Approvable letter for NDA#20372 stipulated that an efficacy analysis be provided for the subpopulation of patients (181 of 252) on whom angiographies were performed. The Sponsor complied (although the data base, for several reasons, was reduced to 160 such patients.) Since the Ischemia/Infarct distinction is not confirmable through angiography, the Sensitivity analysis which would most closely parallel the analysis implied in the table above would be based on a straightforward, subject level, concordance criterion, wherein concordance obtains whenever, simultaneously, Images reveal a coronary defect, and angiography reveals stenosis. This subject level concordance determination does not require that the defect be located where the stenosis would predict it to be. The Sensitivity results for this subset analysis are presented in the table directly below:

Table(b)
Overall Diagnostic Outcome Amended NDA
(Sensitivity percentages with Angiography as Standard of Truth)

	THALLIUM		MYOVIEW	
ISCHEMIA	Reader#1	Reader#2	Reader#1	Reader#2
Study 1 (98 patients;84 with stenosis)	85%	64%	79%	68%
Study 2 (62 patients;58 with stenosis)	79%	86%	76%	81%

The Amended NDA was approved. Labeling incorporates Table(a).

Remarks concerning Table(a) and Table(b):

(1): The expression "Overall Diagnostic Outcome" in Table(a) above has no clear statistical meaning. It would be more accurate to read these percentages as Sensitivities with respect to Final Clinical Diagnosis of Infarct or Ischemia.

(2): The population underlying the percentages in Table(a) is not specified. It could be subjects or vessels. It would make more sense if it were vessels since any particular subject could present with both Infarct and Ischemia. Moreover, the actual numbers of patients/vessels used in the determination of these percentages are not specified.

(3): The percentages themselves are not especially impressive, and nothing in this table addresses Specificity.

(4): The Indication includes the claim that Myoview is useful in the delineation of regions of reversible myocardial ischemia. Given the design of the trials, this claim would appear to be predicated, at the very least, upon the ability of Myoview to differentiate Ischemia from Infarct. This claim for the differential capacity of Myoview, if it is to be supported by table(a), would consist in similar performances of Myoview vs Thallium in Image identification of Infarct, given a Final Clinical Diagnosis of Infarct, along with similar performances of Myoview vs Thallium in Image identification of Ischemia, given a Final Clinical Diagnosis of Ischemia. As the table reveals, blinded Thallium reads are somewhat more successful in the determination of Ischemia than are blinded Myoview reads.

(5): Table(b), derived from the NDA Amendment submission, provides some evidence that the Angiography based Sensitivities for Myoview and Thallium reads are comparable to the "final clinical diagnosis" based Sensitivities obtained in the original submission (as displayed in Table(a).)

(B): Current Myoview Pharmacologic Stress/Rest Clinical Trials:

The Sponsor has provided two, small sample, Pivotal Phase IIIB prospective Clinical trials in support of the proposed Indication. The Sponsor has also provided summaries from several studies culled from the literature, along with copies of the publications themselves. All of these studies will be discussed in considerable detail later on in this review. For purposes of this Overview, a brief description of this material will be provided directly below:

The two Pivotal trials involved a total of 83 evaluable patients who underwent Dipyridamole induced Pharmacologic Stress. Myoview SPECT Images were obtained in both trials, along with Thallium Images in the smaller of the trials. In both trials Coronary Angiography was provided as a Standard of Truth, with Arterial Disease defined as 50% or greater stenosis in a major coronary artery, and with Coronary Disease in a coronary area defined as presence of a perfusion defect under stress imaging. (The more detailed diagnosis of Ischemia – reversible defect - was defined as a difference in the level of perfusion defect, stress vs rest, for any coronary area.) The trials were not powered with respect to any statistical hypotheses. Effectively, for Primary Endpoint Analyses, Concordances between Myoview Images and Angiography (and, when available, between Thallium Images and Angiography) were evaluated, at Subject and Vessel Levels, and the appropriate and standard statistical measures – Sensitivities, Specificities, Kappas, etc, - were reported. There were also several Secondary Endpoint Analyses which were dedicated to distinguishing Infarct from Ischemia. In these latter analyses, Angiography played no role, and the evidence for the validity of the distinctions Myoview provided for Infarct versus Ischemia were either self corroboratory, or corroborated by Thallium Reads, when available.

Supporting Literature Studies:

The Sponsor submitted several papers from the recently published literature on pharmacologic Stress/Rest Myoview SPECT Imagings which, a priori, might be supportive of the extension of the indication of Myoview SPECT Imaging from its previous limitation of "Exercise Stress" to the more general "Exercise/pharmacologic Stress." These papers are described in detail in the Medical Review. With two exceptions, they will be treated here much more briefly, and essentially only with regard to their limitations vis a vis incorporation of their data and statistics into the Efficacy Analysis dedicated to the Pivotal Trials. The two exceptions will be given a more thorough examination, since their designs were judged by this Reviewer as adequate to qualify their inclusion as supporting material for the Sponsor's proposed extended indication.

Literature Studies which did not qualify as Supportive of Efficacy:

Mahmood (1995): This Study employed Adenosine Stress Myoview Imagings with Thallium Rest Imagings, and therefore is unsuitable for Assessment of Induced Stress/Rest Myoview Imagings.

Fukuzawa (1996): The Stress Protocol in this Study combined Dipyridamole Stress with Low-Level Exercise Stress, and therefore is unsuitable for Assessment of Induced Stress/Rest Myoview Imagings.

Takeishi (1998): The Stress Agent was Adenosine Triphosphate, which is not approved.

Thorley (1995): The Stress Agent was Dobutamine, which is not approved.

Adachi (1995): The Stress Agent, Dipyridamole, is an approved agent, but the criterion for Stenosis was set at 75% instead of 50%, and the absence of subject-level data made it impossible to compare or combine the resulting statistics with those of the Pivotal Trials. Moreover, the Vascular Regions were not defined in comparable fashion.

The Two Exceptions:

Cuocolo (1996): This Study qualified for inclusion as a Supportive Study for the Sponsor's new Indication. There were 41 patients, all of whom underwent Angiography. The Stenosis Level for disease was set, as in the Pivotal Trials, at 50%. The Stress Agent was Adenosine, which is an approved agent. The study had the additional feature that Induced Stress was compared to Exercise Stress, thereby allowing for at least some level of assessment regarding similarities in diagnosis for Induced Stress vs Exercise Stress. Two Readers, blinded to Angiography were employed to evaluate the Exercise Stress and Adenosine Stress Images, and the latter two types of images were read independently of one another (although the level of randomization of reads was not specified.) The identification of Arterial Vessels and Coronary Areas was essentially the same as in the Pivotal Trials, and the definition of Concordance of diagnosis between Arterial Vessel Disease Status and Coronary Area Disease Status, along with the definitions for Ischemia vs Infarct, were largely in agreement with the definitions provided in the Pivotal Trials. The only serious concerns regarding the legitimacy of incorporating the results from this publication into the Efficacy Analysis was that the level of detail provided on individual patient efficacy data was limited. That is, although patient-by-patient data was provided on stenosed arteries, no comparably detailed data was provided for diseased coronary territories. This omission limited the reviewer's ability to corroborate the efficacy results.

A second Literature Study which also qualified, in limited fashion, for Inclusion in the Efficacy Analysis is:

Cuocolo (1997): This Study, largely identical in design to Cuocolo(1996), enrolled 26 patients. The principal differences from Cuocolo(1996) are:

(1): Adenosine Stress Myoview Images were compared to Adenosine Stress Echocardiography instead of Exercise Stress. (This comparison will not be exploited in this review.)

(2): The publication included enough "raw data" for independent corroboration of results at least at the subject level.

However:

(3): There is one serious limitation in this study: It shares 7 patients with Cuocolo (1996), and it was not possible to identify these patients. Consequently, a statistically valid pooling of the literature and pivotal trials data would require elimination of one of these literature studies, and this, in fact, was done in the summary section above, so that all inferences relevant to claims and indications will rest on honest data.

Note: The summary section above concentrated on subject level statistics, except in the two cases where segmental infarct vs ischemia distinctions were under examination. The tables directly below provide both vessel level and subject level statistics for Myoview vs the standard of truth of angiography, and they pool the two literature studies, even though the latter share 7 subjects. This somewhat illegitimate pooling plays no role in the formal analysis. Furthermore, since the efficacy claim for disease detection by Myoview, as distinguished from its claim for disease delineation, is being evaluated on a subject level, these vessel level tables serve merely as informal reinforcements to the tables presented in the Summary Section above.

TABLE(IA)
MYOVIEW VS ANGIOGRAPHY - ARTERIAL VESSEL LEVEL
CLINICAL = PR53.006 and PR95-302
LITERATURE = CUOCOLO 1996 and CUOCOLO 1997

ANGIO VS MYOVIEW	CLINICAL			LITERATURE			ALL	
	N	D		N	D		N	D
N	56 (22%)	56 (22%)		75 (37%)	19 (9%)		131 (29%)	75 (17%)
D	50 (20%)	86 (35%)		12 (6%)	95 (47%)		62 (14%)	181 (40%)

N = Normal
D=Diseased

#Vessels(Clinical) = 248 (83 patients)
#Vessels(Literature)=201 (67 patients)

Note: Clinical used Dipyridamole Stress Literature used Adenosine Stress

TABLE(IB)
MYOVIEW VS ANGIOGRAPHY STATISTICAL MEASURES
ARTERIAL VESSEL LEVEL
CLINICAL = PR53.006 and PR95-302
LITERATURE = CUOCOLO 1996 and CUOCOLO 1997

	CLINICAL	LITERATURE	ALL
SENS	61%	83%	71%
SPEC	53%	86%	68%
PPV	63%	89%	74%
NPV	50%	80%	64%
ACC	57%	85%	69%
KAPPA	.14	.70	.37
PREV	57%	57%	57%

TABLE(IIA)
MYOVIEW VS ANGIOGRAPHY - SUBJECT LEVEL
CLINICAL = PR53.006 and PR95-302
LITERATURE = CUOCOLO 1996 and CUOCOLO 1997

ANGIO VS MYOVIEW	CLINICAL		LITERATURE		ALL	
	N	D	N	D	N	D
N	4 (5%)	3 (4%)	3 (4%)	2 (3%)	7 (5%)	5 (3%)
D	9 (11%)	67 (81%)	0 (0%)	62 (93%)	9 (6%)	129 (86%)

N = Normal
D=Diseased

#Patients(Clinical) = 83
#Patients(Literature)=67

Note: Clinical used Dipyridamole Stress
Literature used Adenosine Stress

TABLE(IIB)
MYOVIEW VS ANGIOGRAPHY STATISTICAL MEASURES
SUBJECT LEVEL
CLINICAL = PR53.006 and PR95-302
LITERATURE = CUOCOLO 1996 and CUOCOLO 1997

	CLINICAL	LITERATURE	ALL
SENS	96%	97%	96%
SPEC	31%	100%	44%
PPV	88%	100%	93%
NPV	44%	60%	58%
ACC	86%	97%	91%
KAPPA	.36	.75	.47
PREV	84%	92%	89%

Section (III): Detailed Description of the Clinical Trials

Pivotal Trial #1 Protocol P95-302 Phase IIIB

Title: Comparison of Dipyridamole-201-Thallium with Dipyridamole -Technetium – 99m- Tetrofosmin SPECT Imaging in Patients with Angiographically Confirmed Coronary Artery Disease.

Study Objectives: To compare the Sensitivities and Accuracies of Dipyridamole Thallium SPECT to Dipyridamole Myoview SPECT in Detection of Severity and Extent of Coronary Artery Disease (CAD).

Study Period: 1-16-1996 to 5-8-1996

Design: A Phase IIIB Single-Center, Open-Label Crossover Study to compare Thallium-201 SPECT Perfusion Images to Myoview SPECT Perfusion Images following Dipyridamole-induced pharmacological stress and at Rest/Redistribution. The Standard of Truth for the Principal Efficacy Analysis was Coronary Angiography. All three procedures – Thallium SPECT Imaging, Myoview SPECT Imaging, and Coronary Angiography – were to be completed within a fourteen day period. The various Thallium and Myoview Images were read in random order by two observers (the same two observers for both Thallium and Myoview) blinded to the tracers employed. These two readers then provided a consensus diagnosis. The Standard of Truth -Angiography - was diagnosed unblindedly by the on-site investigators.

Note: Independent reads are preferable to consensus reads.

Population: 26 subjects who met the following two Principal Inclusion Criteria:

(1): Angiographically confirmed Coronary Artery Disease (CAD), defined as 50% or higher stenosis in at least one of the three principal arteries RCA LAD LCx.

(2): Positive Reads for Thallium SPECT Images, defined as the presence of a Perfusion Abnormality at stress in at least one vascular region. These Images were acquired within ten days of the positive Angiography(before or after.)

Overview of Efficacy Analysis/Procedures:

The Primary Efficacy Analysis consisted of blinded Thallium vs Myoview Stress Perfusion Defect Diagnostic Accuracy Comparisons, using Angiography as the Standard of Truth. This Analysis was statistically evaluated via Concordance of diagnoses between Arterial Vessels and correlated Vascular Areas. The correlation was defined as follows:

Vascular Area(1)=Inferior Region, was identified with Arterial Vessel RCA
Vascular Area(2)=Anterior/Septal Region, was identified with Arterial Vessel LAD
Vascular Area(3)=Lateral Region, was identified with Arterial Vessel LCx

A Vascular Area was considered to have a perfusion defect if and only if it presented a perfusion abnormality on SPECT Images at stress.

A Vessel (Coronary Artery - RCA, LAD, LCx) was considered diseased if it revealed at least one lesion of stenosis>=50% on Angiography.

Concordance between a Vascular Area and the corresponding Coronary Artery occurred if the artery was diseased and the Vascular Area had a perfusion defect, or, if the artery was not diseased and the vascular area revealed no perfusion defect.

Using this criterion of Concordance, the various standard statistical measures – Sensitivity, Specificity, etc - were calculated.

Note: Concordance, as described above, provides analyses on a *Vessel Level.* Additionally, Concordance, and the consequent Sensitivities, Specificities, etc, were determined at the *Subject Level.* On this level, concordance of disease occurs provided any of the three vascular Areas has a perfusion defect and, simultaneously, any of the three arterial vessels presents with 50% or greater Stenosis, while concordance of health occurs if all Vascular Areas reveal no Perfusion Defects and all Arterial Vessels are free of significant (>50%) Stenosis. The insensitivity of this type of concordance to disease localization would appear to disqualify it from consideration as a support for indications wherein localization of disease constitutes a specific claim.

Other Efficacy Analyses:

Thallium SPECT Images vs Myoview SPECT Images were also analyzed with respect to defect classifications. These classifications, arrived at by comparison of Perfusion Defect Levels at stress vs rest, were:

Ischemic if a Vascular Area was scored abnormal at stress and at least partially reversible at rest.

Scar (Infarct) if a Vascular Area was scored abnormal at stress and partially reversible or fixed at rest.

This Efficacy Analysis – ischemia vs infarct - has limitations. First, the classifications are not verifiable with respect to the Standard of Truth of Angiography. That is, Angiography does not provide criteria for distinctions between Ischemia and Infarct. Consequently, Thallium becomes the Standard of Truth against which Myoview would be assessed for this Endpoint. Although this criterion for verification of the infarct vs ischemia distinction was prominent in the previous NDA for Exercise Stress, its relevance here is circumscribed by the fact that there are only 26 patients in this first Pivotal Trial, and Thallium is not used in the second Pivotal Trial. Nonetheless, in the Results Section, the comparison of Thallium with Myoview will be examined.

Pivotal Trial #2 Protocol P53.006 Phase IIIB

Title: An Open-Label Study to Evaluate the Use of a One-Day, Dipyridamole/Technetium- 99m-Tetrofosmin Imaging Protocol in the Assessment of Coronary Artery Disease.

Study Objectives:

(1): To determine the Sensitivity, Specificity, and Predictive Accuracy for Detection of CAD using Dipyridamole/Myoview SPECT Imaging.

(2): To determine the ability of Dipyridamole/Myoview SPECT Imaging to predict the Location and Severity of CAD.

Study Period: 4-08-1993 to 12-07-1993

Design: A Phase IIIB, three Center, Open-Label Study to evaluate a one-day Pharmacological Stress Dipyridamole/Myoview SPECT Imaging Protocol in Assessment of CAD. There were no comparators employed in the Study. The Standard of Truth for the Principal Efficacy Analysis was Coronary Angiography, which was to be performed within two months of the Myoview Imaging. The coronary angiography data was evaluated by a blinded, experienced angiographer. The SPECT Images were interpreted by consensus of three blinded readers.

Population: 64 subjects, of whom 58 were included in the final Efficacy Analysis (all 64 were included in the Safety Analysis.) The patients had to meet the following Inclusion Criteria:

Subjects were 30 years of age, or older, and were referred for the evaluation of known or suspected CAD, and must have undergone Coronary Angiography within two months of Test Drug administration.

Efficacy Analysis Background: The Principal Efficacy Analysis appears to have been based, more or less, on concordance of diagnoses between the Coronary Area/Arterial Vessel identifications as described above for P95-302.

Note:
As remarked earlier, the Standard of Truth of Angiography is appropriate for validation of disease only, and for localization of disease, but not for the further classification of disease as Ischemia or Infarct. Claims for Myoview's ability to make such distinctions, if based on evidence provided by this particular pivotal trial, would appear to be self-corroborating.

Section (IV): Supporting Tables:

The tables presented below provide further detail on Vessel and Subject Level Analyses.

Vessel Level

TABLE (IA)
MYOVIEW VS ANGIOGRAPHY BY ARTERIAL VESSEL
PROTOCOL 53.006
(58 Subjects)

ANGIO VS	LAD			LCX			RCA			ALL	
MYOVIEW	N	D		N	D		N	D		N	D
N	12	9		26	15		8	1		46	25
D	15	22		7	10		24	25		46	57

N = Normal
D=Diseased
ALL= LAD+LCX+RCA

TABLE (IB)
STATISTICAL MEASURES MYOVIEW VS ANGIOGRAPHY
(Vessel Level 174 Vessels)
PROTOCOL 53.006

	LAD	LCX	RCA	ALL
SENS	71%	40%	96%	70%
SPEC	44%	79%	25%	50%
PPV	60%	59%	51%	55%
NPV	57%	63%	89%	65%
ACC	59%	62%	57%	59%
KAPPA	.16	.20	.20	.10
PREV	53%	60%	57%	59%

TABLE (IIA)
MYOVIEW VS ANGIOGRAPHY BY ARTERIAL VESSEL
PROTOCOL 95-302
(25 Subjects)

ANGIO VS MYOVIEW	LAD			LCX			RCA			ALL	
	N	D		N	D		N	D		N	D
N	5	13		4	17		1	1		10	31
D	0	7		0	4		4	18		4	29

TABLE (IIB)
STATISTICAL MEASURES MYOVIEW VS ANGIOGRAPHY
(75 Vessels)
PROTOCOL 95-302

	LAD	LCX	RCA	ALL
SENS	35%	19%	95%	48%
SPEC	100%	100%	20%	71%
PPV	100%	100%	82%	88%
NPV	28%	19%	50%	24%
ACC	48%	32%	79%	53%
KAPPA	.18	.07	.02	.06
PREV	80%	84%	79%	81%

TABLE (IIC)
SEGMENTAL AGREEMENT MYOVIEW VS THALLIUM
(325 Segments)
PROTOCOL 95-302

TL/MYO	NORMAL	ISCHEMIA	INFARCT
NORMAL	212 (65%)	7 (2%)	5 (1%)
ISCHEMIA	12 (4%)	42 (13%)	20 (6%)
INFARCT	9 (3%)	6 (2%)	12 (4%)

Note: Kappa = .61

TABLE (IIIA)
MYOVIEW VS ANGIOGRAPHY BY ARTERIAL VESSEL
(26 Subjects)
CUOCOLO (1997)

ANGIO VS MYOVIEW	LAD			LCX			RCA			ALL	
	N	D		N	D		N	D		N	D
N	5	4		12	2		13	3		30	9
D	0	17		2	10		2	8		4	35

TABLE (IIIB)
STATISTICAL MEASURES MYOVIEW VS ANGIOGRAPHY
(78 Vessels)
CUOCOLO (1997)

	LAD	LCX	RCA	ALL
SENS	81%	83%	73%	80%
SPEC	100%	86%	87%	88%
PPV	100%	83%	80%	90%
NPV	56%	86%	81%	77%
ACC	85%	85%	81%	83%
KAPPA	.31	.34	.30	.33
PREV	81%	46%	42%	56%

TABLE (IVA)
MYOVIEW VS ANGIOGRAPHY BY ARTERIAL VESSEL
(41 Subjects)
CUOCOLO (1996)

ANGIO VS	LAD			LCX			RCA			ALL	
MYOVIEW	N	D		N	D		N	D		N	D
N	8	3		22	2		15	5		45	10
D	0	30		2	15		6	15		8	60

TABLE (IVB)
STATISTICAL MEASURES MYOVIEW VS ANGIOGRAPHY
(123 Vessels)
CUOCOLO (1996)

	LAD	LCX	RCA	ALL
SENS	91%	88%	75%	86%
SPEC	100%	92%	71%	85%
PPV	100%	88%	71%	88%
NPV	73%	92%	75%	82%
ACC	85%	85%	73%	85%
KAPPA	.81	.79	.47	.70
PREV	80%	41%	49%	57%

TABLE (IVC)
SEGMENTAL AGREEMENT ADENOSINE STRESS VS EXERCISE STRESS
(902 Segments)
CUOCOLO(1996)

ADENOSINE/EXERCISE	NORMAL	REVERSIBLE	NON-REVERSIBLE
NORMAL	548 (61%)	23 (3%)	13 (1%)
REVERSIBLE	26 (3%)	62 (7%)	1 (1%)
NON-REVERSIBLE	8 (1%)	12 (1%)	199 (22%)

Note: Kappa=.80

TABLE(V)
STATISTICS ON THE FOUR STUDIES AND THEIR COMBINATION
VESSEL LEVEL

	PR 53.006 (N=58)	PR 95-302 (N=25)	CUOCOLO (96) (N=41)	CUOCOLO(97) (N=26)	COMBINED (N=150)
SENS	70%	48%	86%	80%	71%
SPEC	50%	71%	85%	88%	68%
PPV	55%	88%	88%	90%	74%
NPV	65%	24%	82%	77%	64%
ACC	59%	53%	85%	83%	72%
KAPPA	.20	.10	.70	.33	.37
PREV	59%	79%	57%	56%	57%

Note: N = # Subjects (#Vessels=3x#Subjects)

Subject Level

TABLE (VIA)
MYOVIEW VS ANGIOGRAPHY BY SUBJECT

ANGIO VS MYOVIEW	PR53.006			PR95-302			COUCOLO (1997)			CUOCOLO (1996)	
	N	D		N	D		N	D		N	D
N	4	2		0	1		2	2		1	0
D	9	43		0	24		0	22		0	40

TABLE (VIB)
STATISTICAL MEASURES MYOVIEW VS ANGIOGRAPHY
Subject Level

	PR 53.006 (N=58)	PR 95-302 (N=25)	CUOCOLO(97) (N=26)	CUOCOLO (96) (N=41)	COMBINED (N=150)
SENS	96%	96%	92%	100%	96%
SPEC	31%	---	100%	100%	58%
PPV	83%	0%	100%	100%	93%
NPV	67%	100%	50%	100%	58%
ACC	81%	96%	92%	100%	91%
KAPPA	.33	---	---	---	---
PREV	78%	100%	92%	98%	89%

Section (V): Conclusions

For the overall analysis based on the two small pivotal trials, and one independent literature study, Pharmacologic Stress/Rest Myoview SPECT Imagings revealed Subject Level diagnostic Sensitivities comparable to the Sensitivities previously obtained for Exercise Stress/Rest Myoview SPECT Imagings. In particular, Sensitivity is somewhat improved over previous sensitivities obtained in Exercise Stress Myoview studies, although disease definitions are slightly different. The small subject level sample sizes available for Specificity analyses preclude the possibility of drawing inferences for this measure.

Pharmacologic Stress/Rest Myoview SPECT Imagings provide coronary area disease distinctions (Infarct vs Ischemia) consistent with those determined by Exercise Stress/Rest Myoview SPECT Imagings when the pharmacologic stress agent is adenosine (Small SampleLiterature Study.) Pharmacologic Stress/Rest Myoview SPECT Imagings provide coronary area disease distinctions (Infarct vs Ischemia) consistent with those determined by Pharmacologic Stress/Rest Thallium SPECT Imagings when the pharmacologic stress agent is Dipyridamole (Small Pivotal Trial Study.). The presentation of similar consistency between pharmacologic and exercise stress Myoview SPECT Image statistics when dipyridamole is the stress agent has yet to be investigated. All of these comparisons of coronary area disease delineations involve large numbers of coronary segments but small numbers of patients. All of these comparisons involved consensus blind reads, although the different image types were read independently of one another. The small sample sizes involved render these consistencies in diagnoses suggestive rather than conclusive.

Pharmacologic Stress/Rest Myoview SPECT Imaging diagnoses correlate with the disease status of arterial vessels (stenosed, not stenosed) for about two out of every three vessels. This localization of arterial disease is not necessarily as clinically significant as the detection of arterial disease; however, the Sponsor's proposed Labeling clearly makes an Efficacy claim for ———— Furthermore, correct ———— could serve as corroboration for the success of angioplasty if, subsequent to such a therapeutic procedure, Stress/Rest Myoview SPECT Images reveal a change from compromised to normal perfusion for the coronary area supplied by the treated vessel.

The blinded consensus reads common to all these submitted pharmacologic stress studies is not consistent with current FDA guidelines which recommend independent blinded reads. Independent reads would be free of biases which could result from the presence of a dominant reader, and they would also contribute to a profile of the precision to be expected in image diagnoses, both at the Subject and at the Vessel levels. It should be noted, however, that independent read replication of the consensus read Subject level Sensitivities, for example, even if achieved, will not in any way compensate for the current inadequate information on Specificity. Given the enriched nature of the pivotal trial subjects, the latter inadequacy is not addressable with existing data.

S 12/20/99
A G Mucci, Ph. D.
Statistical Reviewer

Concur:

S 12/20/99
Mahboob Sobhan, Ph. D.
Acting Team Leader

S 12/20/99
Michael Welch, Ph. D.
Acting Deputy Director

Cc: Archival NDA#20-372
HFD-160/E Jones/S Loewke/N Arnstein
HFD-160/P Stewart
HFD-160/File Copy
HFD-715/E Nevius/M Welch/M Sobhan/A Mucci

STATISTICAL REVIEW AND EVALUATION

NDA# 20372 Supplemental Application SE1-003 –A2

Sponsor: Nycomed-Amersham (Medi-Physics)

Drug: Myoview (Tc99m Tetrofosmin for Injection)

Indication: Imaging of the Myocardium

Document Date: May 23 2001

PDUFA Date: November 23 2001

Medical Officer: Nelson Arnstein, M.D.

Statistical Reviewer: A G Mucci, Ph.D.

Project Manager: Pat Stewart

Keywords: NDA Review; Clinical Studies; Diagnostic Clinical Trials

Section(0): Overview
Nycomed's earlier NDA#20372 SE1-003 proposed an extension of Myoview's current indication for Exercise Stress SPECT Imaging of the Myocardium to a more inclusive indication for Exercise/ Pharmacologic Stress SPECT Imaging of the Myocardium. The more inclusive indication can take at least two forms: a restricted indication for patients highly suspect for disease, [redacted] NDA #20372 SE1-003 consisted of two small sample clinical trials of patients highly suspect for disease – clinical trials PR53.006 and PR95-302. The clinical trials data was supplemented with several supporting literature studies. Both trials included Angiography as a Standard of Truth. Both trials focused on Sensitivities and Specificities of Myoview with respect to Angiography; the smaller of these trials included Thallium as a comparator. Analyses were conducted by both the Sponsor and the statistical reviewer at both the subject and the vessel level. The FDA review of NDA#20372 SE1-003 concluded that this submission was inadequate for several reasons, prominent among which were (1): the use of consensus reads rather than independent blinded reads of the SPECT Images, and (2): the enriched nature of the patient sample which was not representative of the population likely to undergo pharmacologic Stress/Rest SPECT Imaging. The FDA approvable letter stipulated that a minimal (though not necessarily sufficient) condition for a restricted approval would be a blinded re-read of the clinical trials data. The Sponsor has partially complied with the FDA approvable Letter stipulations by providing independent blinded re-reads of the original data (Supplement NDA#20372 SE1-003-A2). The sponsor has also resubmitted a large number of published papers along with letters from nuclear medicine physicians in support of the validity of a "subject level" analysis of sensitivity and specificity for the SPECT reads.

These re-read data, which are presented in the review below, can, at best, only address the viability of claims for an indication restricted to patients highly suspected for disease. The limited analyses performed in this review, which are largely captured in the three tables below, will focus on claims for restricted indications (enriched population) since the available data from trials PR53.006 and PR95-302 are insufficient for investigations of efficacy for a more representative population. In statistical terms, the data provides reasonable sample sizes for the investigation of sensitivity claims, but inadequate sample sizes for specificity claims. Thus, an efficacy indication whose justification rests primarily on sensitivity should make explicit mention of the fact that the population investigated in support of the indication was a population significantly at risk. This proviso is captured in the italicized portion of the Proposed Indication listed below. For purposes of orientation, the current and proposed restricted indications, are both presented.

Current Approved Indication (Exercise Stress):
Myoview is indicated for the scintigraphic imaging of the myocardium following separate administrations under exercise and resting conditions. It is useful in the d*elineation of regions of reversible myocardial ischemia* in the presence or absence of infarcted myocardium.

Proposed Extended Indication#1(Restricted Population):

The limited analysis presented in this review addresses only one question: Do the blinded rereads present reasonable evidence that pharmacologic stress imaging with Myoview provides subject level sensitivities comparable to those provided by exercise stress imaging with Myoview and also with pharmacologic stress imaging with Thallium? The three tables below provide the statistics on which the answers to this question are based. Table(I) presents subject level Myoview sensitivities, specificities and accuracies for PR53.006. Table(II) presents subject level Myoview and Thallium sensitivities for PR95-302. Table(III) utilizes results found in Table(I) and Table(II) to provide comparisons of pharmacologic stress Myoview imaging subject level sensitivities with subject level sensitivities achieved for exercise stress Myoview(approved) and for pharmacologic stress Thallium (approved). Comparisons are limited to sensitivities since subject level specificities in the current pharmacologic stress Myoview trials are based on only 11 subjects. *It should be understood that, at the subject level, concordance of positive findings between SPECT images and angiography requires only that both SPECT and angiography detect abnormalities, and not that the angiographically determined abnormalities be located in vessels suggested as likely by the locations of the perfusion defects seen on SPECT.*

Table (I)
Reviewer's Statistics For PR53.006 Reads
Myoview Efficacy Statistics with Respect to Angiography
(95% Confidence Intervals)

READ	SUBJECT LEVEL (N = 49 ; Diseased Patients = 38 ; Healthy Patients = 11)		
	SENS	SPEC	ACC
Consensus from previous reads	.97 (.91, 1.0)	.36 (.11,.69)	.84 (.74, .94)
New Reader#1	.79 (.66, .92)	.55 (.23, .83)	.73 (.60, .86)
New Reader#2	.82 (.70, .94)	.45 (.17,.77)	.73 (.60, .86)
New Reader#3	.50 (.34, .66)	.82 (.48, .98)	.57 (.43, .71)

Table (II)
Reviewer's Statistics For PR95-302 Reads
Myoview and Thallium vs Angiography
(95% Confidence Interval)

READ	SUBJECT LEVEL (N= 19 ; Diseased Patients = 19)	
	Sensitivity Myoview	Sensitivity Thallium
Consensus from previous reads	.95 (.85, 1.0)	.95 (.85, 1.0)
New Reader#1	.68 (.47, .89)	.84 (.67, 1.0)
New Reader#2	.68 (.47, .89)	.79 (.60, .98)
New Reader#3	.74 (.54, .94)	.89 (.75, 1.0)

TABLE(III)
Subject Level Sensitivity Comparisons
Current Re-Read Results vs Previous Myoview and Thallium Results
(95% Confidence Interval)

Results from Exercise Stress Myoview NDA (Approved) (Sample Size =142 Subjects)		Results from Pharmacologic Stress Thallium NDA (Approved) (Sample Size = 1100 Subjects)	Results from Current Re-Read Pharmacologic Stress Myoview NDA (Sample size = 57 Subjects)	
Myoview	Thallium	Thallium	Myoview	
.75	.78	.85	.75* (.64 , .86)	.79** (.68 , .90)

Comments :

* and ** : The lower Pharmacologic Stress Myoview Sensitivity (.75) was calculated by averaging over Reader#1 in PR53.006 and Reader#2 in PR95-302. The higher Pharmacologic Stress Myoview Sensitivity was calculated by averaging over Reader#2 in PR53.006 and Reader#3 in PR95-302. This procedure provides for the smallest and the largest sensitivities that can be determined from the combining of the two studies. (We are considering Reader#3 from PR53.006 as an outlier.)

Note that if the "true" sensitivity of Myoview pharmacologic stress imaging were the same as the Thallium figure, namely .85, then the probability that our sample of 57 reads would produce a sensitivity of .75 or less would be prob = .04. If the true sensitivity of Myoview pharmacologic stress imaging were close to the Thallium figure, say .80, then the probability that our sample of 57 reads would produce a sensitivity of .75 or less would be prob = .24. Thus, we would reject, at the .05 level, a one-sided hypothesis that Myoview has a sensitivity of at least .85, while we would not reject, at the .05 level, a one sided hypothesis that Myoview has a sensitivity of at least .80. Consequently, it is reasonable to conclude that pharmacologic stress Myoview imaging provides subject level sensitivities comparable to exercise stress Myoview imaging, but these sensitivities are somewhat weaker than those provided by pharmacologic stress Thallium imaging.

Conclusions:

Myoview subject level sensitivities on the re-reads are comparable to subject level sensitivities attained by Myoview with exercise stress, but somewhat weaker than the subject level sensitivities reported for Thallium with pharmacologic stress. No conclusions regarding specificities are possible, due to sample size limitations. Consequently, proposed indications should stress the enriched nature of the actual population that has been investigated.

/S/

A G Mucci, Ph. D. 11/20/01
Statistical Reviewer

Concur

/S/ 11/20/01
Michael Welch, Ph. D.

Cc: Archival NDA#20-372
HFD-160/E Jones/S Loewke/N Arnstein
HFD-160/P Stewart
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