CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW

CLINICAL STUDIES

NDA:	NDA 22161
Drug Name:	Regadenoson (CVT3146)
Indication:	Adjunct to Radionuclide Myocardial Perfusion Imaging
Applicant:	CV Therapeutics Incorporated
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1. EXECUTIVE SUMMARY

1.1. Conclusions and Recommendations

The sponsor, CVT Therapeutics provided two identically designed Phase III trials for the evaluation of non-inferiority in perfusion defect diagnoses of Rest/Regadenoson Stress SPECT MPI to the Comparator diagnostic of Rest/Adenosine Stress SPECT MPI. The objective was to demonstrate the non-inferiority of the stress agent Regadenson to the approved stress agent Adenosine in SPECT MPI detection of reversible perfusion defects in patients undergoing Rest/pharmacologic Stress SPECT imaging.

The protocol that was utilized for the evaluation of diagnostic non-inferiority centered on comparisons of the levels of agreement in diagnostics between two successive Adenosine scans and corresponding levels of agreement in diagnostics between an Adenosine scan and a Regadenoson scan. The logic behind these comparisons was that if diagnostics with Regadenoson resembled diagnostics derived with Adenosine to the same extent as successive sets of diagnostics with Adenosine resembled one another, then Regadenoson was a viable alternative to Adenosine. The Sponsor provided a prospectively specified novel measure of agreement for evaluation of the non-inferiority claim. The non-inferiority claim was met in both trials for the Sponsor's proposed measure; moreover, several other comparisons as well as the reviewer's sensitivity analyses for similarity in diagnoses showed consistent results.

Based on the statistical evaluation of the information submitted by the sponsor, the statistical reviewer concludes that the data provides substantial evidence of efficacy of Regadenoson and recommends approval for the registration of this product from efficacy standpoint.

1.2 Overview of Clinical Studies

NDA22161 provided two identically designed Phase III trials:

CVT5131: Start Date October 2003 ; Completion Date August 2006

CVT5132: Start Date April 2004 : Completion Date June 2006

Essentials Elements of the Identical Trials:

Common Design: These were Phase III, randomized, double-blind studies of the approved pharmacologic stress agent (Adenosine) versus the Test pharmacologic stress agent (Regadenoson) in which patients referred for a clinically indicated Rest/ pharmacologic Stress SPECT MPI underwent an Initial Rest/pharmacologic Stress SPECT MPI with Adenosine as the Stress agent and with Myoview or Cardiolite as the imaging agent. Subsequently, patients were randomized to either a repeat Rest/Stress SPECT MPI with Adenosine, or to a Rest/Stress SPECT MPI with Regadenoson. The randomized imaging sessions followed the same imaging protocol and used the same

imaging agent as the initial session. The ratio for randomization was 2 to 1 in favor of Regadenoson.

Common Objective: The objective was to demonstrate that the concordance levels in diagnostics between the Regadenoson and the Adenosine scans were similar to the concordance levels in diagnostics between the two sequential Adenosine scans. Concordance was measured with the Sponsor's agreement statistic.

Common Primary Endpoint: The median count across three independent blinded readers of the detected number of reversible perfusion defects.

Common Statistical Objective:
To demonstrate that the Adenosine-Regadenoson level of agreement for numbers of reversible defects was non-inferior to the Adenosine-Adenosine level of agreement. The Non-Inferiority null and alternative hypotheses were:

H_o: Regadenoson/Adenosine Agreement –Adenosine/Adenosine Agreement $\geq$ -.1333
H_a: Regadenoson/Adenosine Agreement –Adenosine/Adenosine Agreement < -.1333

Results:
Study CVT5131 enrolled 2446 patients, of whom 1211 (50%) completed the study and were included in the efficacy analyses. The principal reason for termination was exclusion through a risk assessment: Subjects whose initial Adenosine scan classification was "low risk" were excluded once this class achieved sufficient representation. The risk assessment was based on the on-site initial Adenosine scan assessment, which was relayed to a core center where the decision to exclude was made if the assessment was "low risk" after sufficient numbers of "low risk" patients had been enrolled. Most of the completers (>80%) had a history of CAD and were equally represented in both study arms.

The Sponsor's primary efficacy measure for comparison of agreement levels between the arms was .61 for the Adenosine-Adenosine Arm (Comparator) and it was .62 for the Adenosine-Regadenoson Arm (Test). The lower bound of the 95% confidence interval for the difference of .01 was greater than the proposed non-inferiority limit resulting in the rejection of the null hypothesis. Several additional secondary endpoint comparisons between the arms were conducted for other diagnoses: Wall Motion scores; SSS scores; myocardial region diagnoses. In all cases the objective was to show that the levels of replicability of the scores achieved in the Adenosine-Regadenoson Arm were consistent with the levels of replicability achieved in the Adenosine-Adenosine Arm. This objective was informally met in all comparisons (no formal statistical testing was performed on these secondary endpoints.) The secondary endpoint comparisons are important contributors to a cumulative body of evidence in favor of similarity of diagnostic performance in trials such as this, where a standard of truth is absent.

The inference from the primary and secondary analyses was that Regadenoson was not inferior to Adenosine as a stress agent for SPECT Rest/Stress MPI perfusion diagnostics.

Study CVT5132 enrolled 1023 patients, of whom 784 (77%) completed the study and were included in the efficacy analyses. The principal reason for termination was exclusion through risk assessment, as described above in case of study CVT5131. Most of the completers (>80%) had a history of CAD and were equally represented in both study arms.

The Sponsor's primary efficacy measure for comparison of agreement levels between the arms was.64 for the Adenosine-Adenosine Arm (Comparator) and it was .63 for the Adenosine-Regadenoson Arm (Test). The lower bound of the 95% confidence interval for the difference of - .01 was greater than the proposed non-inferiority limit resulting in the rejection of the null hypothesis. As with Study CVT5131, several additional, secondary endpoint comparisons between the arms were conducted - Wall Motion scores ; SSS scores, myocardial region diagnoses. In all cases the objective was to show that the levels of replicability of the scores achieved in the Adenosine-Regadenoson Arm were consistent with the levels of replicability achieved in the Adenosine-Adenosine Arm. Again, this objective was informally met in all comparisons

The conclusion inferred from the primary and secondary analyses was that Regadenoson was not inferior to Adenosine as a stress agent for SPECT Rest/Stress MPI perfusion diagnostics.

1.3 Statistical Issues and Findings

As stated in Setion 1.2, the Sponsor proposed the following general criterion for efficacy of the pharmacological stress agent Regadenoson:

SPECT Rest/Regadenoson Stress MPI provides similar diagnostic success for detection of perfusion defects as does (approved) SPECT Rest/Adenosine Stress MPI.

Since the composition of the patient population in these trials did not permit universal application of the truth standard of angiography, Sensitivity and Specificity comparisons of Regadenoson stress diagnostics to Adenosine stress diagnostics could not be considered as measures of efficacy of Regadenoson.. The Sponsor therefore had to make direct comparisons of (unverified) perfusion diagnostics between the rest/stress procedures using an approved stress agent, Adenosine and the rest/stress procedures using Regadenoson. The approach consisted of measuring levels of diagnostic concordance between two successive Adenosine scans and showing that the levels achieved were effectively replicated in diagnostics between an Adenosine scan and a subsequent Regadenoson scan. Thus, similar diagnostic success was interpreted as similar levels of replicability in diagnostics.

The critical issues concerning similarity in diagnostics for these trials were:

*Issue(a): **The Sponsor's Agreement Measure**:* The Sponsor provided a measure of concordance, or replicability, between perfusion results achieved on successive SPECT scans. The similarity of SPECT Regadenoson diagnostics to SPECT Adenosine diagnostics was then assessed in the primary analysis as the non-inferiority of the agreement level achieved in the Adenosine-Regadenoson scan sequence to the agreement level achieved in the successive Adenosine scans sequence. The concern here is both with the appropriateness of the proposed measure of agreement and with the focus of the primary analysis on the reversible perfusion defects alone. Consequently, alternative comparisons of perfusion defect diagnostics, along with comparisons for alternative diagnostics, such as Wall Motion and Summed Stress Scores, were undertaken to provide important supportive evidence for the Sponsor's claims.

As for the appropriateness of the proposed measure of agreement, the technical investigation of this reviewer (given in Appendix) shows that this measure can be expressed as an average of conditional concordances and that the principal advantage provided by this measure is its insensitivity to category prevalences. This reviewer also compared this measure to the more standard Kappa measure and showed that there is a straightforward linear relationship between Kappa and the Sponsor's measure. Thus, if Kappa is an acceptable concordance measure, so is the Sponsor's measure.

*Issue(b): **Non-Inferiority Level**:* Under the assumption that the agreement measure captures the notion of concordance, there remains the issue of the suitability of the non-inferiority limit (set at - .133) for acceptable differences in agreement. The Sponsor proposed the non-inferiority limit as the analogue of a non-inferiority limit appropriate for the Kappa statistic. The sponsor's supporting arguments for the analogy were somewhat obscure. The Sponsor inferred -.20 from the published literature as an acceptable non-inferiority limit for Kappa (Landis & Koch: Biometrics 33, 159-174 ; 1977) and then applied the derived -.133 as the appropriate non-inferiority limit for the proposed measure by applying the linear relationship between Kappa and their measure. However, this reviewer has not found final and convincing evidence that Kappa values that differ by less than .20 should be considered essentially equivalent as measures of concordance or replicability.

This issue was resolved by the reviewer by examining, in the trials under review, the similarities in diagnostic outcomes between the arms, not only in terms of the Sponsor's agreement measure, but also in terms of all other measures investigated by both the Sponsor and the Reviewer. These analyses trump possible reservations about the non-inferiority margin. That is, in addition to the Sponsor's having met the "not completely convincing" criterion of non-inferiority for a reasonable measure of agreement for diagnoses of perfusion defects, there is a cumulative body of evidence strongly trending towards similarity of diagnostic performance for several other measures involving several other endpoints – Wall Motion, SSS, etc.

Thus after careful consideration of these issues, but only in light of actual trial results, the reviewer concludes that these issues do not raise significant problems.

2. INTRODUCTION

2.1 Overview

NDA22161 provided two identically designed Phase III trials:

CVT5131: Start Date October 2003 ; Completion Date August 2006
CVT5132: Start Date April 2004 : Completion Date June 2006

Common Design:
Phase III, randomized, double-blind study of the approved pharmacologic stress (Adenosine) versus the Test pharmacologic agent (Regadenoson)
in patients referred for a clinically indicated SPECT MPI using Adenosine.

Common Randomization Procedure
Patients underwent an Initial Rest/Stress SPECT MPI with Adenosine as the Stress agent and with Myoview or Cardiolite as the imaging agent. Subsequently, patients were randomized to either a repeat Rest/Stress SPECT MPI with Adenosine, or to a Rest/Stress SPECT MPI with Regadenoson. The randomized imaging sessions followed the same imaging protocol and used the same imaging agent as the initial session. The ratio for randomization was 2 to 1 in favor of Regadenoson.

Common Objective:
To demonstrate that the strength of Agreement between Regadenoson and Adenosine SPECT images was not inferior to the strength of Agreement between two sequential Adenosine SPECT images. The Agreement Measure, calculated in each arm, was a measure of concordance in numbers of reversible perfusion defects found between the initial scan and the randomized scan. The objective was to demonstrate that the concordance levels between the Regadenoson and the Adenosine scans were similar to the concordance levels between the two sequential Adenosine scans.

Common Primary Endpoint: The median count across three independent blinded readers of the detected number of reversible perfusion defects.

Common Statistical Objective:
To demonstrate that the Adenosine-Regadenoson level of Agreement for numbers of reversible defects was non-inferior to the Adenosine-Adenosine level of Agreement. The Non-Inferiority hypothesis was:

H_0: Regadenoson/Adenosine Agreement –Adenosine/Adenosine Agreement > -.1333
H_a: Regadenoson/Adenosine Agreement –Adenosine/Adenosine Agreement < -.1333

Results:
Study#5131 enrolled 2446 patients, of whom 1211 (50%) completed the study and were included in the efficacy analyses. The principal reason for termination was exclusion through risk assessment: Subjects whose Initial Adenosine scan classification was Low

Risk were excluded once this class achieved sufficient representation. Most of the completers (>80%) had a history of CAD and were equally represented in both study arms.

The Sponsor's primary efficacy measure for comparison of agreement levels between the arms scored at level .61 for the Adenosine-Adenosine Arm (Comparator) and scored at level .62 for the Adenosine-Regadenoson Arm (Test). The difference of .01 was consistent with the proposed non-inferiority limit. Several additional, secondary endpoint comparisons between the arms were conducted - Wall Motion scores ; SSS scores, myocardial region diagnoses. In all cases the objective was to show that the levels of replicability of the scores achieved in the Adenosine-Regadenoson Arm were consistent with the levels of replicability achieved in the Adenosine-Adenosine Arm. This objective was informally met in all comparisons (no formal statistical testing was performed on secondary endpoints.) These secondary endpoint comparisons are contributors to a cumulative body of evidence in favor of similarity of diagnostic performance in trials such as this, where a standard of truth is absent. The conclusion inferred from the primary and secondary analyses was that Regadenoson was not inferior to Adenosine as a stress agent for SPECT Rest/Stress MPI perfusion diagnostics.

Study#5132 enrolled 1023 patients, of whom 784 (77%) completed the study and were included in the efficacy analyses. The principal reason for termination was exclusion through risk assessment: Subjects whose Initial Adenosine scan classification was Low Risk were excluded once this class achieved sufficient representation. Most of the completers (>80%) had a history of CAD and were equally represented in both study arms.

The Sponsor's primary efficacy measure for comparison of agreement levels between the arms scored at level .64 for the Adenosine-Adenosine Arm (Comparator) and scored at level .63 for the Adenosine-Regadenoson Arm (Test). The difference of - .01 was consistent with the proposed non-inferiority limit. Several additional, secondary endpoint comparisons between the arms were conducted - Wall Motion scores ; SSS scores, myocardial region diagnoses. In all cases the objective was to show that the levels of replicability of the scores achieved in the Adenosine-Regadenoson Arm were consistent with the levels of replicability achieved in the Adenosine-Adenosine Arm. This objective was informally met in all comparisons (no formal statistical testing was performed on secondary endpoints.) These secondary endpoint comparisons are contributors to a cumulative body of evidence in favor of similarity of diagnostic performance in trials such as this, where a standard of truth is absent. The conclusion inferred from the primary and secondary analyses was that Regadenoson was not inferior to Adenosine as a stress agent for SPECT Rest/Stress MPI perfusion diagnostics.

2.2 Data Sources

The data source for this review is: **\\CDSESUB1\EVSPROD\NDA022161\0000**

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Detailed Overview of Design

The primary goal of the NDA#22161 trials was to demonstrate that:

Rest/Stress SPECT MPI with Regadenoson pharmacologic stress provided similar perfusion diagnostics to Rest/Stress SPECT MPI with Adenosine pharmacologic stress.

Two identical clinical trials – CVT5131 and CVT5132 – were dedicated to this goal.

The common statistical design employed to establish this goal was the following:

(1): All patients underwent an Initial Adenosine Rest/Stress SPECT MPI

(2): Patients were then randomized to undergo either:

(a): A second Adenosine Rest/Stress SPECT MPI (Adenosine-Adenosine Arm)

(b): A Regadenoson Rest/Stress SPECT MPI (Adenosine- Regadenoson Arm)

Blinded read diagnostics from three independent readers were acquired for all scans. Each reader read both the Initial Scan and the randomized Scan.

The principal endpoints collected from these reads were as follows:

1> Segment level determinations of presence/absence of reversible perfusion defects
2> SSS (Summed stress scores)
3> WM (Wall Motion) diagnostics

For each endpoint the median read result over the three readers was chosen as the representative score for comparisons of results between the two arms. Thus, if the three independent reads for reversible perfusion defects determined, respectively, 5 , 8, and 6 such defects for the Initial Scan and 4, 7, and 9 such defects for the Randomized Scan, then the paired read used for statistical analyses was Initial = 6 ; Randomized = 7. It is to be noted here that the paired reads used for statistical analyses do not necessarily come from the same reader.

The objective was to show that the pairs of median scores – Initial versus Randomized - within the Adenosine- Regadenoson Arm were statistically similar to the pairs of median scores – Initial versus Randomized – within the Adenosine-Adenosine Arm.
The reversible perfusion defect scores were chosen for primary analyses; SSS and WM scores were used in secondary analyses.

The primary statistical endpoint was an agreement measure between the Initial Scan reads and the Randomized Scan reads. This Agreement measure was first applied to each arm separately, and then the two results were compared for similarity. Thus, the objective was not to use the measure to evaluate consistency between an initial and a randomized read, but, rather, to demonstrate that, with this measure as the standard, the two study arms provided similar levels of consistency between their initial and final scans.

Definition of the Agreement Measure:

For each subject , and for both the Initial Scan and the Randomized Scan, the median number of reversible perfusion defects was reduced to a category result:

1= L = Low Number of reversible defects = 0 or 1 defect

2 = M = Moderate Number of defects = 2, 3 or 4 defects

3 = U = Large Number of defects = 5 or more defects

Thus, for each subject, one of nine possibilities obtained between the Initial Read and the Randomized Read: (L, L) , (L, M) , . . . (U, U). The general table of frequencies from which the measure of Agreement comparisons was generated took the form below, where:

AI= Initial Adenosine Read ; AF = Final Adenosine Read ; R = Regadenoson Read

Table 1: Definition of Agreement Measure

	Adenosine-Adenosine						Adenosine-Regadenoson			
	AF= 1	AF= 2	AF= 3				R = 1	R = 2	R = 3	
AI = 1	N(1,1)	N(1,2)	N(1,3)	$N_I(1)$		AI = 1	M(1,1)	M(1,2)	M(1,3)	$M_I(1)$
AI = 2	N(2,1)	N(2,2)	N(2,3)	$N_I(2)$		AI = 2	M(2,1)	M(2,2)	M(2,3)	$M_I(2)$
AI = 3	N(3,1)	N(3,2)	N(3,3)	$N_I(3)$		AI = 3	M(3,1)	M(3,2)	M(3,3)	$M_I(3)$
	$N_R(1,1)$	$N_R(1,2)$	$N_R(1,3)$	N			$M_R(1,1)$	$M_R(1,2)$	$M_R(1,3)$	M

Then, the Measure of Agreement was defined as follows:

Adenosine-Adenosine Agreement

$$A^*_C = (1/3) \{ N(1,1)/N_I(1) + N(2,2)/N_I(2) + N(3,3)/N_I(3) \}$$

Adenosine-Regadenoson Agreement

$$A^*_T = (1/3) \{ M(1,1)/M_I(1) + M(2,2)/M_I(2) + M(3,3)/M_I(3) \}$$

Difference in Agreement:

$D^* = A^*_T - A^*_C$ = Difference in weighted average of agreement levels

Primary Statistical Objective:

To show that $D^* = A^*_T - A^*_C$ was small enough to conclude Non-Inferiority of Regadenoson to Adenosine as a stress agent for Rest/Stress SPECT MPI.

The Sponsor's proposed criterion for Non-Inferiority was that the lower bound of a 95% confidence interval for D^* exceeds - .133.

The Sponsor provides a somewhat obscure rationale for this criterion. Of greater importance than this rationale is the fact that the actual 3x3 cell percentages derived from the data for the tables above are so similar from arm to arm and trial to trial that the criterion pales in comparison. The cell by cell results will be examined in the discussions of results by clinical trial presented below.

However, it is noted here that the criterion, whatever its intrinsic merits, was met for both trials. Moreover, several alternative analyses for diagnostic similarity between the study arms, presented in the results section below, provide strong supportive evidence for the Sponsor's claims.

3.1.2 Presentation and Analysis of Efficacy Results

The presentation below will provide comparisons between the Adenosine-Adenosine Arm and the Adenosine-Regadenoson Arm from five perspectives:

(1): The Sponsor's Primary Reversible Defect Agreement Measure

(2): The Reviewer's Myocardial Region 2x2 Defect/No-Defect Analysis

(3): The Reviewer's Wall Motion 2x2 Defect/No-Defect Analysis

(4): The Sponsor's Sensitivity/Specificity Results for Angiography Subjects

(5): The Reviewer's comparisons of Initial versus Randomized SSS Regressions

These comparisons will be carried out on a Study- by-Study basis, and then Comparison (1) will be reconsidered with respect to a Chi- Squared Test for Homogeneity with the two studies combined.

The Reviewer's principal inference from the several data analyses is that the particular primary endpoint comparisons are of less significance than the fact that the tables used for the derivation of the primary measure of agreement, and the tables used for the

various alternative displays of outcomes, are very similar between the Test and Comparator arms. In such circumstances as these, similarities between arms for the scalar primary measure of Agreement derived from tables are reflective of more fundamental cell-by-cell similarities between the tables.

The Efficacy analyses will be preceded by presentations of patient disposition results and demographic results. The demographic results will include statistics on relevant patient history.

Results for Study 5131 are as follows:

Table 2: Patient Disposition – Study 5131

Study#5131	N
Number Originally Enrolled and Receiving Baseline Scan	2446
Number Terminating Before Study Completion	1235 (50%)
Reasons for Termination:	
Baseline scored Low after Closure for Low Category Enrollment	961 (39%)
Adverse Events	41 (2%)
Non-Compliance/Elective Withdrawal/Lost to Follow-Up	139 (6%)
Death	1
All Other Categories	93 (4%)
Number Completing Study	1211 (50%)

Remark: The percentage of patients completing the study was half (50%) of the patients originally enrolled. It should be noted that the principal reason for exclusion was:

Baseline scored Low Category after Closure for Low Category Enrollment (39%)

The protocol incorporated a Core Center check on Initial Scan classifications for reversible defects by an independent agent (not one of the blinded readers) who excluded Low Risk patients from the analysis who were enrolled subsequent to a Low-Risk quota. The intention here was to achieve a relative balance among risk levels.

Table 3: Demographics and Imaging Protocol Statistics – Study 5131

	Adenosine-Adenosine	Adenosine-Regadenoson
Age: Mean (Sigma)	66 (11)	67 (11)
< 65 N (%)	172 (46%)	300 (40%)
≥65 N (%)	200 (54%)	441 (60%)
Male N (%)	270 (73%)	534 (72%)
Female N (%)	102 (27%)	207 (28%)
WT (Kg) : Mean (Sigma)	84 Kg (18 Kg)	85 Kg (18 Kg)
Race: N (%)		
Caucasian	270 (73%)	544 (73%)
Hispanic	49 (13%)	90 (12%)
Black	28 (8%)	46 (6%)
Asian	20 (5%)	53 (7%)
Other	5 (1%)	8 (1%)
Probability of CAD		
< 10%	37 (10%)	105 (14%)
10% - 90%	51 (14%)	97 (13%)
> 90%	284 (76%)	539 (73%)
Cardiovascular History		
CAD	305 (82%)	617 (83%)
Angina (Typical)	249 (67%)	481 (65%)
Infarction	182 (49%)	317 (43%)
CABG/PTCA/Stenting	209 (56%)	407 (55%)

Primary Efficacy Results

The Primary Efficacy statistics were derived from the 3x3 table below.

Table 4: Primary Efficacy Results for Study 5131

	Adenosine-Adenosine					Adenosine-Regadenoson			
	AR= 1	AR= 2	AR= 3			RR = 1	RR = 2	RR = 3	
AI = 1	218 (59%)	34 (9%)	3 (1%)	255 (69%)	AI = 1	436 (59%)	64 (9%)	5 (1%)	505 (68%)
AI = 2	24 (6%)	47 (13%)	13 (3%)	84 (22%)	AI = 2	55 (7%)	94 (13%)	23 (3%)	172 (23%)
AI = 3	7 (2%)	12 (3%)	14 (4%)	33 (9%)	AI = 3	8 (1%)	27 (4%)	29 (9%)	64 (9%)
	249 (67%)	93 (25%)	30 (8%)	372		499 (67%)	185 (25%)	57 (8%)	741

(AI = Initial Adenosine ; AR = Randomized Adenosine RR = Randomized Regadenoson)

The Agreement Scores derived from these tables, along with their difference, and the 95% CI for the difference follow:

A^*_C = Adenosine - Adenosine Agreement = .61

A^*_T = Adenosine – Regadenoson Agreement = .62 ;

$D^* = A^*_T - A^*_C$ = Difference = .01

95% Two-sided CI for D^* = (-.07 , +.09)

Note that the lower limit for the 95% two-sided CI for D^* equals - .07 and exceeds the non-Inferiority boundary of -.133 leading to the conclusion of Non-Inferiority.

Remark: The similarity in Agreement levels is not an endorsement of the value of these levels as measures of agreement. Note also that the straightforward agreement in each table (sum of diagonal cell percentages) is:

Diagonal Agreement for Adenosine-Adenosine = 76%
Diagonal Agreement for Adenosine-Regadenoson = 81%

Secondary Efficacy Results

Comparisons of Perfusion Defect Detections at the Myocardial Region Level

The next comparison is the Reviewer's comparison of 2x2 tables for the two study arms where the cross-classifications are Initial versus Randomized diagnoses for reversible perfusion defects at a myocardial region level. No formal statistics will be done on this table since there could be significant within-patient correlations among diagnoses from

region to region. However, the cell-by-cell similarities between the two tables speak for the equivalence of diagnostic performance between arms at this region level.

Table 5: Myocardial Region Level Comparisons For Reversibles- Study 5131

	Randomized = Adenosine			Randomized = Regadenoson	
	Randomized = 0	Randomized = 1		Randomized = 0	Randomized = 1
Initial = 0	812 (73%)	67 (6%)		1613 (72%)	139 (6%)
Initial = 1	82 (7%)	152 (14%)		160 (7%)	314 (14%)

(Adenosine – Adenosine Arm versus Adenosine –Regadenoson Arm)
(A Region is read as either No Reversibles =0 or as At Least One Reversible = 1)
(The three segments (LAD, LCX , RCA) are combined.)

Wall Motion Comparisons

Comparisons of Adenosine-Adenosine versus Adenosine- Regadenoson for WM Abnormalities for Study5131 are presented below. The myocardium was partitioned into five regions, and each region was classified as Normal = 0 , or as Abnormal = 1. The table presents the data on a WM region level. As the tables indicate, there was essential identity between Adenosine-Adenosine cell frequencies and Adenosine-Regadenoson cell frequencies.

Table 6: Region Level Comparisons For WM Abnormalities – Study 5131

STUDY5131					
	Randomized = Adenosine			Randomized = Regadenoson	
	Randomized = 0	Randomized = 1		Randomized = 0	Randomized = 1
Initial = 0	1401 (76%)	98 (5%)		2822 (76%)	156 (4%)
Initial = 1	78 (4%)	278 (15%)		153 (4%)	579 (16%)

(Adenosine – Adenosine Arm versus Adenosine –Regadenoson Arm)
(A Region is read as either Abnormal = 1 or Normal = 0)
(The Five Regions are combined.)

Sensitivity/Specificity Results for Study 5131

A small percentage of patients (5%) underwent Angiography. The Sensitivities and Specificities at a myocardial region level for these patients are presented below.
It is to be understood that the apparent poor Sensitivity in both arms could be the result of the inexact mapping between arteries and myocardial regions, and should therefore not be construed as poor performance. The more critical feature is the consistency in results from arm to arm.

Sensitivity for Adenosine-Adenosine Arm

Initial Sensitivity	N = 174 segments	Sensitivity = .34
Randomized Sensitivity	N = 174 segments	Sensitivity = .38

Sensitivity for Adenosine-Regadenoson Arm

Initial Sensitivity	N = 324 segments	Sensitivity = .39
Randomized Sensitivity	N = 324 segments	Sensitivity = .40

Specificity for Adenosine-Adenosine Arm

Initial Specificity	N = 117 segments	Specificity = .87
Randomized Specificity	N = 117 segments	Specificity = .87

Specificity for Adenosine-Regadenoson Arm

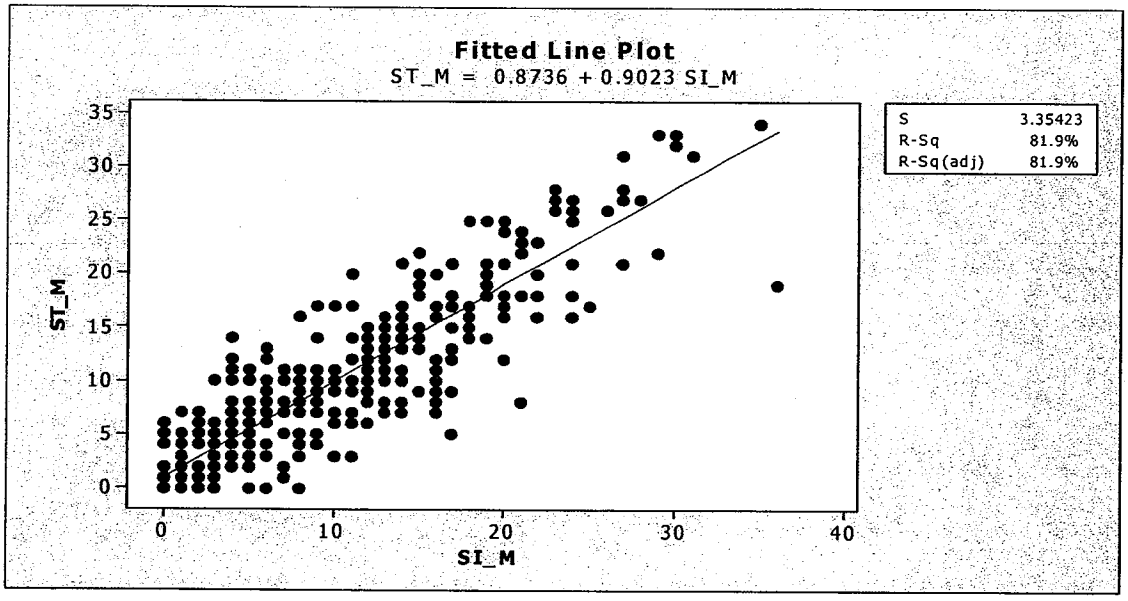
Initial Specificity	N = 228 segments	Specificity = .86
Randomized Specificity	N = 228 segments	Specificity = .85

Comparisons of Initial Scan and Randomized Scan SSS Results

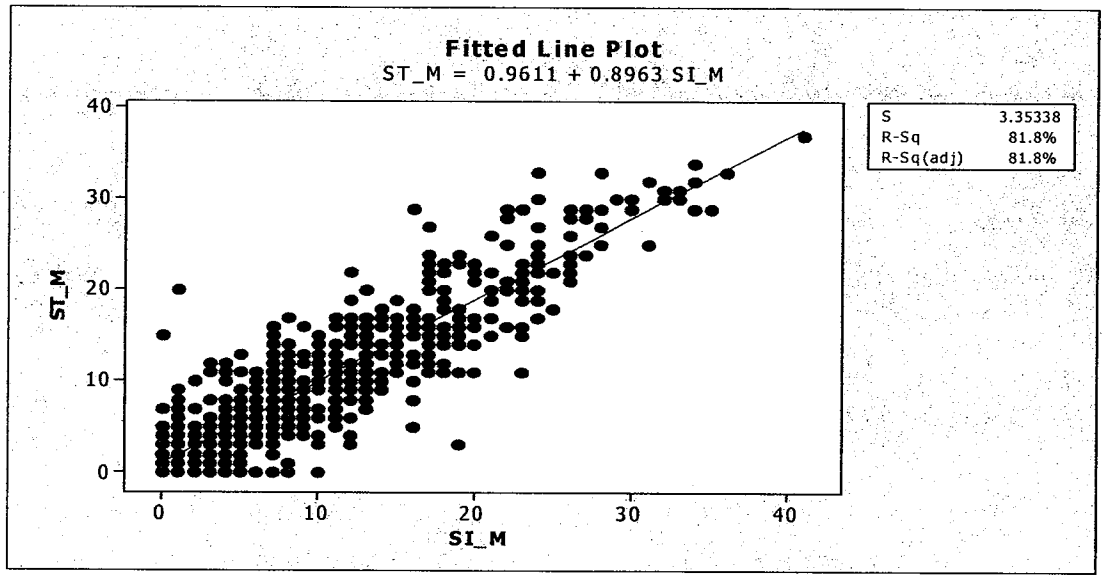
Regressions between SSS scores on the Initial Scan and the Randomized Scan are presented below. Note:

Randomized Adenosine = .90*Initial Adenosine + .87 ; Correlation = .90
Randomized Regadenoson = .90*Initial Adenosine + .90 ; Correlation = .90

Study5131
Regression of Randomized Adenosine SSS versus Initial Adenosine SSS
ST_M = Median Randomized SSS ; SI_M = Median Initial SSS



Study5131
Regression of Randomized Regadenoson SSS versus Initial Adenosine SSS
ST_M = Median Randomized SSS ; SI_M = Median Initial SSS



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The results for Study 5132 are as follows:

Table 7: Patient Disposition- Study 5132

Study 5132	N
Number Originally Enrolled and Receiving Baseline Scan	1023
Number Terminating Before Study Completion	239 (23%)
Reasons for Termination:	
Baseline scored Low after Closure for Low Category Enrollment	139 (14%)
Adverse Events	10 (1%)
Non-Compliance/Elective Withdrawal/Lost to Follow-Up	49 (5%)
All Other Categories	41 (4%)
Number Completing Study	784 (77%)

Remark: The percentage of patients completing the study was half (50%) of the patients enrolled. The principal reason for exclusion was:Baseline scored Low Category after Closure for Low Category Enrollment (14%). The protocol incorporated a Core Center check on Initial Scan classifications for reversible defects by an independent agent who excluded those Low Risk patients who were enrolled subsequent to a Low-Risk quota. The intention was to achieve a relative balance among risk levels.

Table 8: Demographics and Imaging Protocol Statistics – Study 5132

	Adenosine-Adenosine	Adenosine-Regadenoson
Age: Mean (Sigma)	64 (11)	64 (12)
< 65 N (%)	126 (49%)	244 (49%)
≥65 N (%)	133 (51%)	255 (51%)
Male N (%)	160 (62%)	330 (66%)
Female N (%)	99 (38%)	169 (34%)
WT (Kg) : Mean (Sigma)	83 Kg (18 Kg)	83 Kg (18 Kg)
Race: N (%)		
Caucasian	202 (78%)	391 (78%)
Hispanic	7 (3%)	25 (5%)
Black	21 (8%)	32 (6%)
Asian	5 (2%)	26 (5%)
Other	24 (9%)	25 (5%)
Probability of CAD		
< 10%	45 (17%)	83 (17%)
10% - 90%	62 (24%)	104 (21%)
> 90%	152 (59%)	312 (63%)
Cardiovascular History		
CAD	170 (66%)	349 (70%)
Angina (Typical)	138 (53%)	308 (62%)
Infarction	88 (34%)	177 (35%)
CABG/PTCA/Stenting	114 (44%)	220 (44%)

Table 9: Primary Efficacy Results for Study 5132

	Adenosine-Adenosine			
	AR= 1	AR= 2	AR= 3	
AI = 1	144 (56%)	20 (8%)	11 (4%)	175 (68%)
AI = 2	22 (8%)	31 (12%)	10 (4%)	63 (24%)
AI = 3	4 (1%)	4 (1%)	13 (5%)	21 (8%)
	170 (66%)	55 (21%)	34 (13%)	259

	Adenosine-Regadenoson			
	RR = 1	RR = 2	RR = 3	
AI = 1	270 (54%)	45 (9%)	14 (3%)	329 (66%)
AI = 2	46 (9%)	50 (10%)	26 (5%)	122 (24%)
AI = 3	5 (1%)	11 (2%)	32 (6%)	48 (10%)
	321 (64%)	106 (22%)	72 (14%)	499

(Parentheticals are % of Total Sample)
(AI = Initial Adenosine ; AR = Randomized Adenosine RR = Regadenoson)

The Agreement Scores derived from these tables, along with their difference, and the 95% CI for the difference follow:

A^*_C = Adenosine-Adenosine Agreement = .64

A^*_T = Adenosine – Regadenoson Agreement = .63

$\Delta^* = A^*_T - A^*_C$ = Difference = - .01 ;

95% Two-sided CI for Δ^* = (-.11 , +.09)

Note that the lower limit for the 95% two-sided CI for Δ^* equals - .11 and exceeds the non-Inferiority boundary of -.133 leading to the conclusion of Non-Inferiority.

Remark: The similarity in Agreement levels is not an endorsement of the value of these levels as measures of agreement. Note also that the straightforward agreement in each table (sum of diagonal cell percentages) is:

Diagonal Agreement for Adenosine-Adenosine = 75%
Diagonal Agreement for Adenosine-Regadenoson = 70%

The next comparison is the Reviewer's comparison of 2x2 tables for the two study arms where the cross-classifications are Initial versus Randomized diagnoses for reversible perfusion defects at a myocardial region level. No formal statistics will be done on this table since there could be significant within-patient correlations among diagnoses from region to region. However, the cell-by-cell similarities between the two tables speak for the equivalence of diagnostic performance between arms at this region level.

Table 10: Myocardial Region Level Comparisons For Reversibles – Study 5132

	STUDY5132			
	Randomized = 0	Randomized = 1	Randomized = 0	Randomized = 1
Initial = 0	537 (69%)	74 (9%)	1026 (69%)	140 (9%)
Initial = 1	64 (8%)	105 (13%)	130 (9%)	198 (13%)

(Adenosine – Adenosine Arm versus Adenosine –Regadenoson Arm)
(A Region is read as either No Reversibles =0 or as At Least One Reversible = 1)
(The three segments (LAD, LCX , RCA) are combined.)

Wall Motion Comparisons

Comparisons of A-A versus A- R for WM Abnormalities are presented below, by Study and Combined. The myocardium was partitioned into five regions, and each region was classified as Normal = 0 , or as Abnormal = 1. The tables present the data on a WM region level.

Table 11: Region Level Comparisons For WM Abnormalities – Study 5132

	STUDY5132			
	A = 0	A = 1	R = 0	R = 1
Initial = 0	1073 (83%)	40 (3%)	1946 (78%)	92 (4%)
Initial = 1	38 (3%)	149 (11%)	79 (3%)	373 (15%)

(Adenosine – Adenosine Arm versus Adenosine –Regadenoson Arm)
(A Region is read as either Abnormal = 1 or Normal = 0)
(The Five Regions are combined.)

Sensitivity/Specificity Results for Study 5132

A small percentage of patients (2%) underwent Angiography. The Sensitivities and Specificities at a myocardial region level for these patients are presented below.
It is to be understood that the apparent poor Sensitivity in both arms could be the result of the inexact mapping between arteries and myocardial regions, and should therefore not be construed as poor performance. The more critical feature is the consistency in results from arm to arm.

Sensitivity for Adenosine-Adenosine Arm
Initial Sensitivity N = 56 segments Sensitivity = .48
Randomized Sensitivity N = 56 segments Sensitivity = .38

Sensitivity for Adenosine-Regadenoson Arm
Initial Sensitivity N = 117 segments Sensitivity = .49
Randomized Sensitivity N = 117 segments Sensitivity = .49

Specificity for Adenosine-Adenosine Arm
Initial Specificity N = 55 segments Specificity = .69
Randomized Specificity N = 55 segments Specificity = .67

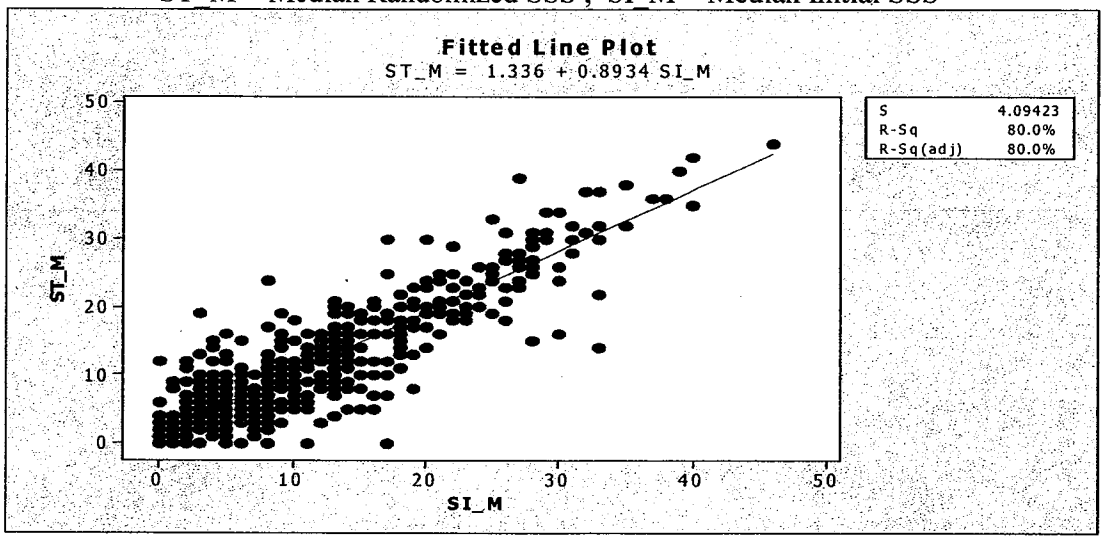
Specificity for Adenosine-Regadenoson Arm
Initial Specificity N = 126 segments Specificity = .75
Randomized Specificity N = 126 segments Specificity = .72

Comparisons of Initial Scan and Randomized Scan SSS Results

Regressions between SSS scores on the Initial Scan and the Randomized Scan are presented below. Note:

Randomized Adenosine = .89*Initial Adenosine + 1.34 ; Correlation = .89
Randomized Regadenoson = .89*Initial Adenosine + 1.39 ; Correlation = .90

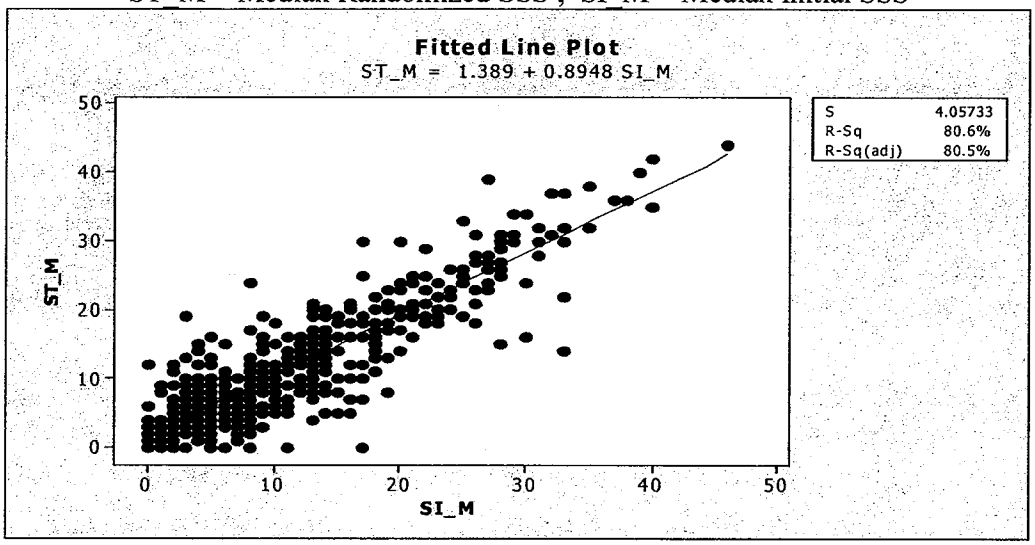
Study5132
Regression of Randomized Adenosine SSS versus Initial Adenosine SSS
ST_M = Median Randomized SSS ; SI_M = Median Initial SSS



Study5132

Regression of Randomized Regadenoson SSS versus Initial Adenosine SSS

ST_M = Median Randomized SSS ; SI_M = Median Initial SSS



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3.2 Evaluation of Safety

There were no significant safety issues. A possible concern was the potential safety effect of the Regadenoson injection, which was not adjusted for weight. The table below provides evidence that there was no significant increase in adverse events by weight for Regadenoson.

Table 12: Combined Studies Principal Adverse Event by Weight

WGT Category (Kg's)	Arm	Agent	N	Angina	Chest Discomfort	Dyspnea
W < 60	A-A	I A	61	6 (10%)	6 (10%)	12 (20%)
		F A	61	7 (11%)	6 (10%)	13 (21%)
	A-R	I A	90	5 (6%)	18 (20%)	18 (20%)
		F R	90	7 (8%)	16 (18%)	29 (32%)
60≤ W < 80	A-A	I A	231	31 (13%)	41 (18%)	55 (24%)
		F A	231	31 (13%)	40 (17%)	53 (23%)
	A-R	I A	497	72 (14%)	74 (15%)	108 (22%)
		F R	497	55 (11%)	58 (12%)	121 (24%)
80≤ W < 100	A-A	I A	267	38 (14%)	38 (14%)	78 (29%)
		F A	267	43 (16%)	46 (17%)	73 (27%)
	A-R	I A	530	75 (14%)	81 (15%)	118 (22%)
		F R	530	48 (9%)	62 (12%)	143 (27%)
100≤ W < 120	A-A	I A	96	12 (13%)	14 (15%)	26 (27%)
		F A	96	15 (16%)	21 (22%)	24 (25%)
	A-R	I A	168	27 (16%)	36 (21%)	56 (33%)
		F R	168	20 (12%)	26 (15%)	59 (35%)
120≤ W	A-A	I A	23	2 (9%)	4 (17%)	10 (43%)
		F A	23	3 (13%)	6 (26%)	10 (43%)
	A-R	I A	52	4 (8%)	8 (15%)	22 (42%)
		F R	52	0 (0%)	6 (12%)	17 (33%)

(I = Initial Scan ; F = Final (Randomized) Scan)

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

The primary endpoint agreement levels are presented in the table below by Age, Race and Gender.

Table 13: Agreement Rates by Subgroups

	N	Adenosine-Adenosine		N	Adenosine-Regadenoson
Study5131 All	371	.62		742	.62
Study5132 All	260	.64		498	.63
AGE					
Study5131 (Age <65)	169	.62		303	.62
Study5131 (Age ≥65)	126	.62		244	.62
Study5132 (Age<65)*	202	.49		439	.62
Study5132 (Age≥65)*	134	.77		254	.65
GENDER					
Study5131 Male	270	.63		534	.63
Study5131 Female	101	.52		208	.54
Study5132 Male	161	.67		329	.65
Study5132 Female	99	.60		169	.55
RACE					
Study5131 Caucasian	270	.63		544	.61
Study5131 Other	101	.61		198	.63
Study5132 Caucasian	203	.67		390	.64
Study5132 Other	57	.55		108	.60

Remark: There is a slight and consistent imbalance in rates by gender within arms (not across arms.) No explanation is forthcoming.

4.2 Other Special/Subgroup Populations

The primary endpoint agreement levels are presented in the table below by CAD Risk as assessed at enrollment.

Table 14: Agreement Rates by CAD Class at Enrollment

	N	Adenosine-Adenosine		N	Adenosine-Regadenoson
Study5131 All	371	.62		742	.62
Study5132 All	260	.64		498	.63
CAD CLASS					
Study5131 Low Risk*	37	.75		105	.58
Study5131 Moderate Risk*	51	.85		96	.51*
Study5131 High Risk	282	.61		541	.63
Study5132 Low Risk	45	.57		83	.64
Study5132 Moderate Risk*	62	.51		104	.68
Study5132 High Risk	153	.68		311	.62

Remark: There is an imbalance between the arms for rates by CAD class. These imbalances are difficult to resolve since they move in different directions for the two trials, and, they disappear once the trial results are combined (see table below.)

Table 15: Agreement Rates By CAD Class - Combined Studies

A-A Arm				A-R Arm	
Low Risk*	82	.65		188	.61
Moderate Risk*	113	.66		200	.60
High Risk	435	.62		852	.63

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5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The similarities in outcomes between the two trials allow for the pooling of results for a more compact overview of the results. Several tables of combined results are presented below.

Table 16: Combined Table For Primary Efficacy Results

	Adenosine-Adenosine					Adenosine-Regadenoson			
	AR= 1	AR= 2	AR= 3			RR = 1	RR = 2	RR = 3	
AI = 1	362 (57%)	54 (9%)	14 (2%)	430 (68%)	AI = 1	706 (57%)	109 (9%)	19 (2%)	834 (67%)
AI = 2	46 (7%)	78 (12%)	23 (4%)	147 (23%)	AI = 2	101 (8%)	144 (12%)	49 (4%)	294 (24%)
AI = 3	11 (2%)	16 (3%)	27 (4%)	54 (9%)	AI = 3	13 (1%)	38 (3%)	61 (5%)	112 (9%)
	419 (67%)	148 (23%)	64 (10%)	631		820 (66%)	291 (24%)	129 (10%)	1240

(Parentheticals are % of Total Sample)
(AI = Initial Adenosine Score ; AR = Randomized Adenosine Score)
(RR = Regadenoson Score)

Note:
The Chi-Square Test for Homogeneity yields $\chi^2_8 = 4.31$, and $P\{ \chi^2_8 \geq 4.31\} = .83$

Remark: This is strong evidence that the two samples are representative of the same distribution. Given this result, any reservations about similarity between performances for the two arms would have to focus on:

The appropriateness of perfusion defect categories as an endpoint.

Therefore, several additional analyses, which focus on similarities between SSS, WM, results, etc, have been carried out. The idea here is to see if these secondary analyses, cumulatively, buffer the Sponsor's claim that the substitution of Regadenoson for Adenosine provides non-inferior Rest/Stress SPECT MPI diagnostics.

Combined Studies Sensitivity/Specificity Results – Region Level

There were 281 patients in Study#5131 and 118 patients in Study#5132 who underwent Angiography. Sensitivity and Specificity were calculated on a Region level for regions (LAD, LCX , RCA) for these patients by defining:

Concordance for Defect:
Artery has≥ 50% Stenosis and matching Myocardial Region has a Perfusion Defect

Concordance for No defect:
Artery has< 50% Stenosis and matching Myocardial Region has no Perfusion Defect

Results:

Sensitivity for Adenosine-Adenosine Arm
Initial Sensitivity N = 230 Regions Sensitivity = .37
Randomized Sensitivity N = 230 Regions Sensitivity = .38

Sensitivity for Adenosine-Regadenoson Arm
Initial Sensitivity N = 441 Regions Sensitivity = .42
Randomized Sensitivity N = 441 Regions Sensitivity = .42

Specificity for Adenosine-Adenosine Arm
Initial Specificity N = 172 Regions Specificity = .81
Randomized Specificity N = 172 Regions Specificity = .81

Specificity for Adenosine-Regadenoson Arm
Initial Specificity N = 354 Regions Specificity = .82
Randomized Specificity N = 354 Regions Specificity = .80

Wall Motion Comparisons

Comparisons of Adenosine-Adenosine versus Adenosine- Regadenoson for WM Abnormalities are presented below, by Study and Combined. The myocardium was partitioned into five regions, and each region was classified as Normal = 0 , or as Abnormal = 1. The tables present the data on a WM region level. As the tables indicate, there was essential identity between Adenosine-Adenosine cell frequencies and Adenosine-Regadenoson cell frequencies.

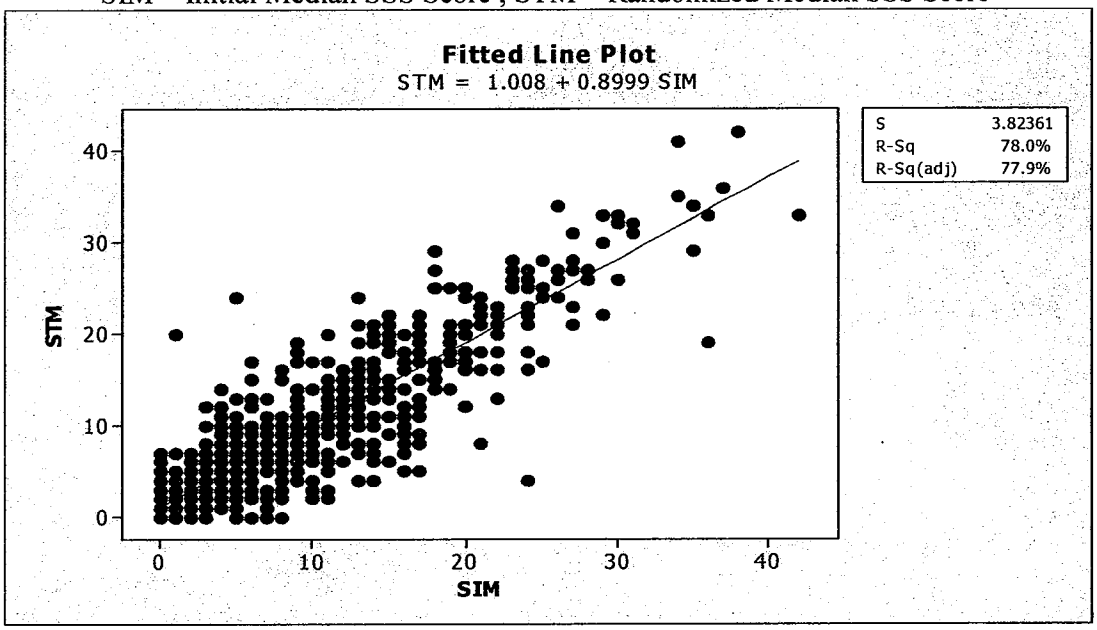
Table 17: Combined Myocardial Region Level Comparisons For WM Abnormalities

COMBINED STUDIES					
	Randomized = 0	Randomized = 1		Randomized = 0	Randomized = 1
Initial = 0	2474 (78%)	138 (4%)		4768 (77%)	248 (4%)
Initial = 1	116 (4%)	427 (14%)		232 (4%)	952 (15%)

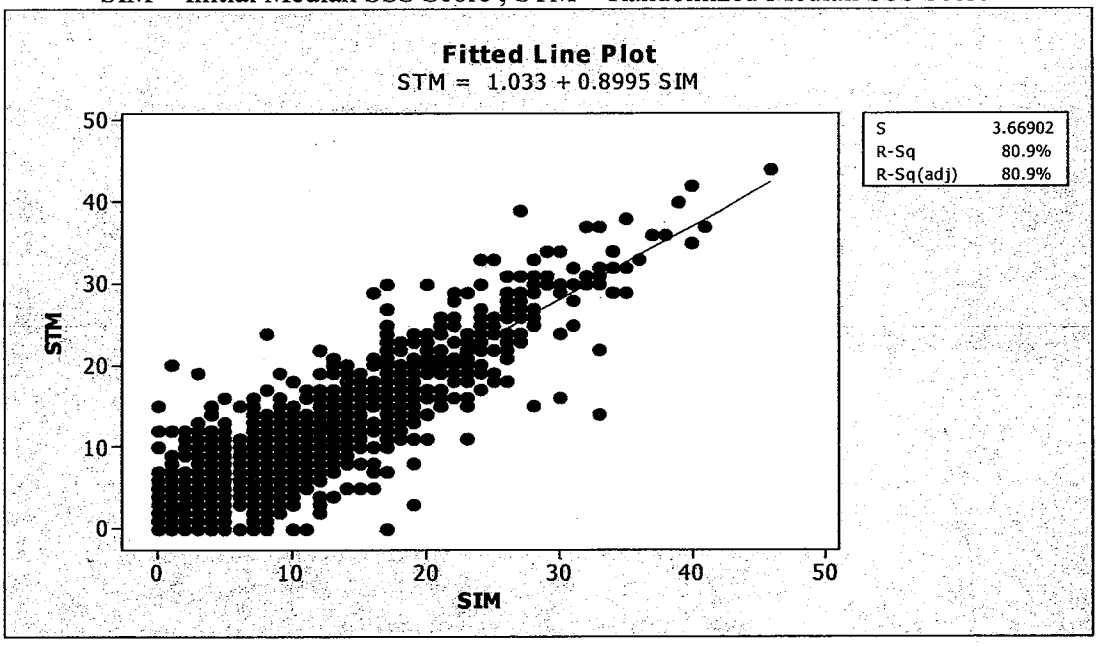
(Adenosine – Adenosine Arm versus Adenosine –Regadenoson Arm)
(A Region is read as either Abnormal = 1 or Normal = 0)
(The Five Regions are combined.)

Comparisons of Arms by SSS Scores

Regression of Randomized Adenosine SSS on Initial Adenosine SSS
SIM = Initial Median SSS Score ; STM = Randomized Median SSS Score



Regression of Randomized Regadenoson SSS on Initial Adenosine SSS
SIM = Initial Median SSS Score ; STM = Randomized Median SSS Score



5.2 Conclusions and Recommendations

The sponsor, CVT Therapeutics provided two identically designed Phase III trials for the evaluation of non-inferiority in perfusion defect diagnoses of Rest/Regadenoson Stress SPECT MPI to the Comparator diagnostic of Rest/Adenosine Stress SPECT MPI. The objective was to demonstrate that SPECT scan detections of reversible perfusion defects for subjects undergoing Rest/Stress with the Sponsor's pharmacological stress agent (Regadenoson) were non-inferior to SPECT scan detections of reversible perfusion defects for subjects undergoing Rest/Stress with an approved pharmacological stress agent(Adenosine).

The protocol that was utilized for the evaluation of diagnostic non-inferiority centered on comparisons of the levels of agreement in diagnostics between two successive Adenosine scans and corresponding levels of agreement in diagnostics between an Adenosine scan and a Regadenoson scan. The logic behind these comparisons was that if diagnostics with Regadenoson resembled diagnostics derived with Adenosine to the same extent as successive sets of diagnostics with Adenosine resembled one another, then Regadenoson was a viable alternative to Adenosine. The Sponsor provided a prospectively specified novel measure of agreement for evaluation of the non-inferiority claim. The non-inferiority claim was met in both trials for the Sponsor's proposed measure; moreover, several other comparisons as well as the reviewer's sensitivity analyses for similarity in diagnoses showed consistent results.

Based on the statistical evaluation of the information submitted by the sponsor, the statistical reviewer concludes that the data provides substantial evidence of efficacy of Regadenoson and recommends approval for the registration of this product from efficacy standpoint.

APPENDIX

Sponsor's Agreement Measure and Its Relationship to Kappa:

For each subject, and for both the Initial Scan and the Randomized Scan, the median number of reversible perfusion defects was reduced to a category result:

1= L = Low Number of reversible defects = 0 or 1 defect

2 = M = Moderate Number of defects = 2, 3 or 4 defects

3 = U = Large Number of defects = 5 or more defects

Thus, for each subject, one of nine possibilities obtained between the Initial Read and the Randomized Read: (L, L) , (L, M) , . . . (U, U). The general table of frequencies from which the measure of Agreement comparisons was generated took the form below, where:

AI= Initial Adenosine Read ; AF = Final Adenosine Read ; R = Regadenoson Read

Table A.1

	Adenosine-Adenosine						Adenosine-Regadenoson			
	AF= 1	AF= 2	AF= 3				R = 1	R = 2	R = 3	
AI = 1	N(1,1)	N(1,2)	N(1,3)	$N_I(1)$		AI = 1	M(1,1)	M(1,2)	M(1,3)	$M_I(1)$
AI = 2	N(2,1)	N(2,2)	N(2,3)	$N_I(2)$		AI = 2	M(2,1)	M(2,2)	M(2,3)	$M_I(2)$
AI = 3	N(3,1)	N(3,2)	N(3,3)	$N_I(3)$		AI = 3	M(3,1)	M(3,2)	M(3,3)	$M_I(3)$
	$N_R(1,1)$	$N_R(1,2)$	$N_R(1,3)$	N			$M_R(1,1)$	$M_R(1,2)$	$M_R(1,3)$	M

Then, the Measure of Agreement was defined as follows:

Adenosine-Adenosine Agreement

$$A^*_C = (1/3) \{ N(1,1)/N_I(1) + N(2,2)/N_I(2) + N(3,3)/N_I(3) \}$$

Adenosine-Regadenoson Agreement

$$A^*_T = (1/3) \{ M(1,1)/M_I(1) + M(2,2)/M_I(2) + M(3,3)/M_I(3) \}$$

Difference in Agreement:

$$D^* = A^*_T - A^*_C$$

The Agreement measures clearly are averages of conditional concordances. For instance, in terms of probabilities:

$A^*_T = (1/3)(\ P\{R = L \mid AI = L\} + P\{R = M \mid AI = M\} + P\{\ R = U \mid AI = U\ \}\ )$

The principal advantage provided by this measure is its insensitivity to category prevalences. A comparison of this measure to the more standard Kappa measure is developed as follows:

First, consider a generalization of the Agreement measure when the diagnoses can take on values, say, $I = 1, 2, \ldots, M$ instead of just three values. Let X and Y be the diagnoses, and let:

D_I = Event that $X = Y = I$; $P_I = P\{\ X = I\ \}$; $Q_I = P\{\ Y = I\ \}$

Then the Sponsor's Agreement formula is: Agreement = $A = (1/M) \sum P\{\ D_I \mid X = I\ \}$

A more general formula , allowing for different weights, is:

(*): $A = \sum \lambda_I P\{\ D_I \mid X = I\ \}$ where $\sum \lambda_I = 1$

Now consider Kappa = K in the same context, and set $\lambda_I = P_I\ (\ 1 - Q_I\ ) / \sum_J P_J\ (\ 1 - Q_J\ )$

Then

(**): $K = \sum \lambda_I\ (\ \{\ P\{\ D_I \mid X = I\ \} - Q_I\ \} / \{\ 1 - Q_I\ \}\ )$

Now if we could choose $P_I = 1/M$, then $\lambda_I = (\ 1 - Q_I\ ) // (\ M - 1\ )$ and we can express the Sponsor's measure **A** as a linear function of K:

$A = \{(M-1)/M\} * K + 1/M$

In the case under consideration, with $M = 3$: $A = (2/3)K + 1/3$

Now, in the case where the strata for categories L, M, U, can be controlled so that each category is as likely as any other category to occur for the Initial Adenosine scan, there is a straightforward linear relationship between Kappa and the Sponsor's measure. Thus, if Kappa is an acceptable concordance measure, so is the Sponsor's measure.

Non-Inferiority Level

If we express differences in Agreement A, namely $D_A = A^*_T - A^*_C$, as differences in Kappa K, denoted $D_K = K_T - K_C$, we'd have

$D_A = (2/3)D_K$

It is here that the Sponsor justifies the value -.133, since this value = - (2/3)*(.20), and the Sponsor infers -.20 from the published literature as an acceptable non-inferiority limit for Kappa. (Landis & Koch: Biometrics 33 159-174 ; 1977). But there is no final and convincing evidence that Kappa values that differ by less than .20 should be considered essentially equivalent as measures of concordance or replicability.

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STATISTICAL REVIEW AND EVALUATION

Stability Studies

NDA/Serial Number:	22- 161/004
Drug Name:	Lexiscan (regadenoson) in 5mLVials and 5mL ANSYR Syringes
Indication:	Pharmacologic Stress Agent for Myocardial Perfusion Imaging
Applicant:	CV Therapeutics, Inc. and Astellas Pharma US, Inc.
Date:	November 30, 2007
Statistical Reviewer:	Roswitha Kelly, M.S., OTS/OB/DB6
Concurring Reviewer:	Yi Tsong, Ph.D., OTS/OB/DB6
Medical Division:	Division of Medical Imaging and Hematology Products, Office of Oncology Drug Products
Chemistry Reviewer:	Jila Boal, Ph.D., OPS/ONDAQ/DPAMS
Project Manager:	Tiffany J. Brown, M.P.H, OND/OODP/DMIHP

Keywords: Regadenoson, drug product, drug substance, stability

Distribution: NDA 22-161/Regadenoson
OND/OODP/DMIHP/T. Brown, M.P.H.
ONDQA/ /J. Boal, Ph.D./
OTS/OB/DB6/R. Kelly/Y. Tsong, Ph.D./S. Machado, Ph.D./T. Saha/R. O'Neill, Ph.D./L. Patrician, M.S.

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1. EXECUTIVE SUMMARY

1.1. Conclusions and Recommendations

The sponsor submitted 18-month stability data for both the drug substance and the drug product. The drug product is packaged as vials and as syringes. The drug substance and the drug product in vials and in syringes have [redacted] registration batches each on stability as well as supportive data.

The sponsor performed the standard statistical analyses for stability data and shelf life estimation. Using the acceptance criteria for assay, [redacted] and Total Impurities appropriate for the drug substance and the drug product, respectively, the sponsor estimated retest periods of at least [redacted] and extrapolated shelf lives of at least [redacted] The reviewer confirmed several of the sponsor's analyses and accepted the remainder of their findings. She agrees with the sponsor, that a [redacted] extrapolated retest period for the drug substance and a 30-month extrapolated shelf life for the drug product is supported based on the data and the appropriate statistical analyses.

1.2. Brief Overview of Stability Studies

The sponsor has [redacted] registration batches of the drug substance on long term stability. The batch sizes ranged from [redacted] and were manufactured in late 2005 by [redacted] The long term study (25°C/60%RH) is planned for [redacted] The main attributes were assay, impurity [redacted] and total impurities and the retest period was estimated using release specifications.

The sponsor has [redacted] registration batches of the drug product on long term stability, [redacted] of which are vials (25°C/60%RH) and [redacted] are syringes (25°C/40%RH). All batches were manufactured at a [redacted] scale, which is [redacted] of the proposed maximum commercial batch size. Each vial batch was stored upright and inverted whereas each syringe batch was stored horizontal and inverted. The vial batches were manufactured by Baxter Pharmaceutical Solutions LLC, Bloomington, IN, and the syringe batches by Hospira, Inc., Rocky Mount, NC. The same attributes as for the drug substance were evaluated but with stability specifications.

1.3. Statistical Issues and Findings

No statistical issues became apparent. The sponsor appeared to follow ICH Q1A(R2) and used an FDA stability program which had been made available to industry many years ago. As the product is a liquid, the sponsor applied two-sided confidence limits when estimating the retest period or expiry based on assay data. Otherwise, one-sided upper confidence limits were employed when the impurities data were analyzed. The reviewer

agreed with the sponsor's analysis approach. She spot-checked the sponsor results and conclusions with several of the data sets. She obtained identical numeric results and came to the same conclusions with respect to the estimated retest period and expiry.

2. INTRODUCTION

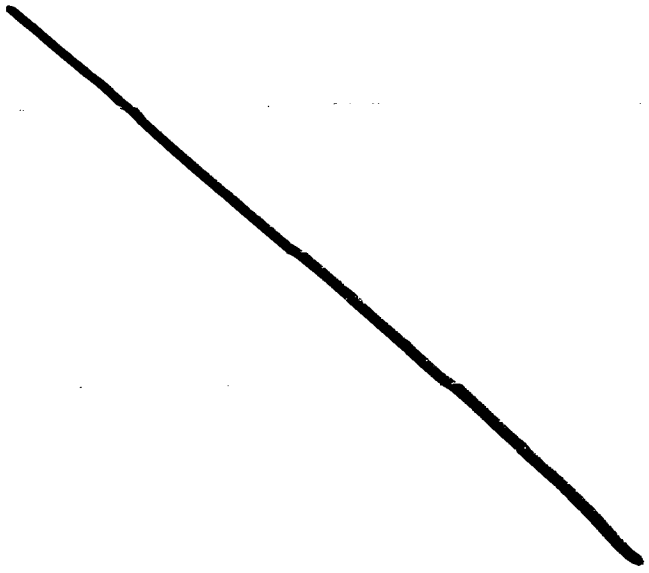
2.1. Overview

This is a statistical evaluation of the 18-month stability data from regadenoson drug substance registration batches and from regadenoson drug product registration batches. The drug product comes in vials and in syringes which are stored long-term at slightly different conditions (25°C/60%RH for vials and 25°C/40%RH for syringes) and positions (upright and inverted for vials and upright and horizontal for syringes). The stability study is planned for [redacted] The attributes which lent themselves to statistical evaluation were assay, impurity [redacted] and total impurities.

2.2. Data Sources

The sponsor submitted the stability data for the drug substance and for the drug product in two SAS transport files. Though minor modifications to the data file were needed (e.g. the results of the attributes were submitted as character variables when they should have been numeric), in general the data files were complete and followed most of the desired format.

3. STATISTICAL EVALUATION



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