Name of Sponsor/Company: Astellas Pharma Global Development, Inc. (APGD)		
Name of Finished Product: Regadenoson		
Name of Active Ingredient: Regadenoson		

SYNOPSIS

Title of Study: A Phase 3b, Open-label, Parallel Group, Randomized, Multicenter Study to Assess Regadenoson Administration Following an Inadequate Exercise Stress Test as Compared to Regadenoson Alone For Myocardial Perfusion Imaging (MPI) Using Single Photon Emission Computed Tomography (SPECT)/3606-CL-3004

Responsible Medical Officer: [redacted] MD, [redacted]

Study Center(s): This study was conducted at 49 contracted sites in a total of 3 countries and regions including the United States (44 sites), Argentina (4 sites) and Peru (1 site).

Publication Based on the Study: None

Study Period: 2 years

Study Initiation Date (Date of First Enrollment): 29 June 2012

Date of Last Patient Last Visit: 05 June 2014

Study Completion Date (Final Data Collection Date for Primary Outcome Measure): 17 December 2014

Phase of Development: Phase 3b

Objectives: The primary objective was to demonstrate that the strength of agreement between SPECT imaging with regadenoson following inadequate exercise stress testing and SPECT imaging with regadenoson alone is not inferior to the strength of agreement between 2 sequential regadenoson SPECT images without exercise.

Secondary objectives included comparing the safety, tolerability and hemodynamic changes when regadenoson is administered following inadequate exercise stress testing to regadenoson given without exercise and comparing SPECT scan agreement and image quality of regadenoson administered following inadequate exercise stress testing to regadenoson given without exercise.

Methodology: This was a multicenter, open-label, parallel design study in patients who have been referred for an exercise or pharmacological stress SPECT MPI test and who met 1 of the following 3 criteria during a Bruce or modified Bruce exercise protocol at visit 2: reached 85% maximum predicted heart rate (MPHR), but were unable to achieve 5 metabolic equivalents (METs); were unable to reach 85% MPHR, but achieved 5 METs; or were unable to reach both 85% MPHR and 5 METs.

Patients were randomized into 1 of 2 groups and underwent 2 SPECT MPI stress images after an initial rest SPECT MPI. In Group 1 (Regadenoson after Peak Exercise [REG APEX]), patients received regadenoson 3 minutes after exercise (in walk recovery) then underwent a stress SPECT MPI at visit 2 (MPI 1 [exercise + regadenoson]) and patients received regadenoson at rest without exercise then underwent a stress SPECT MPI

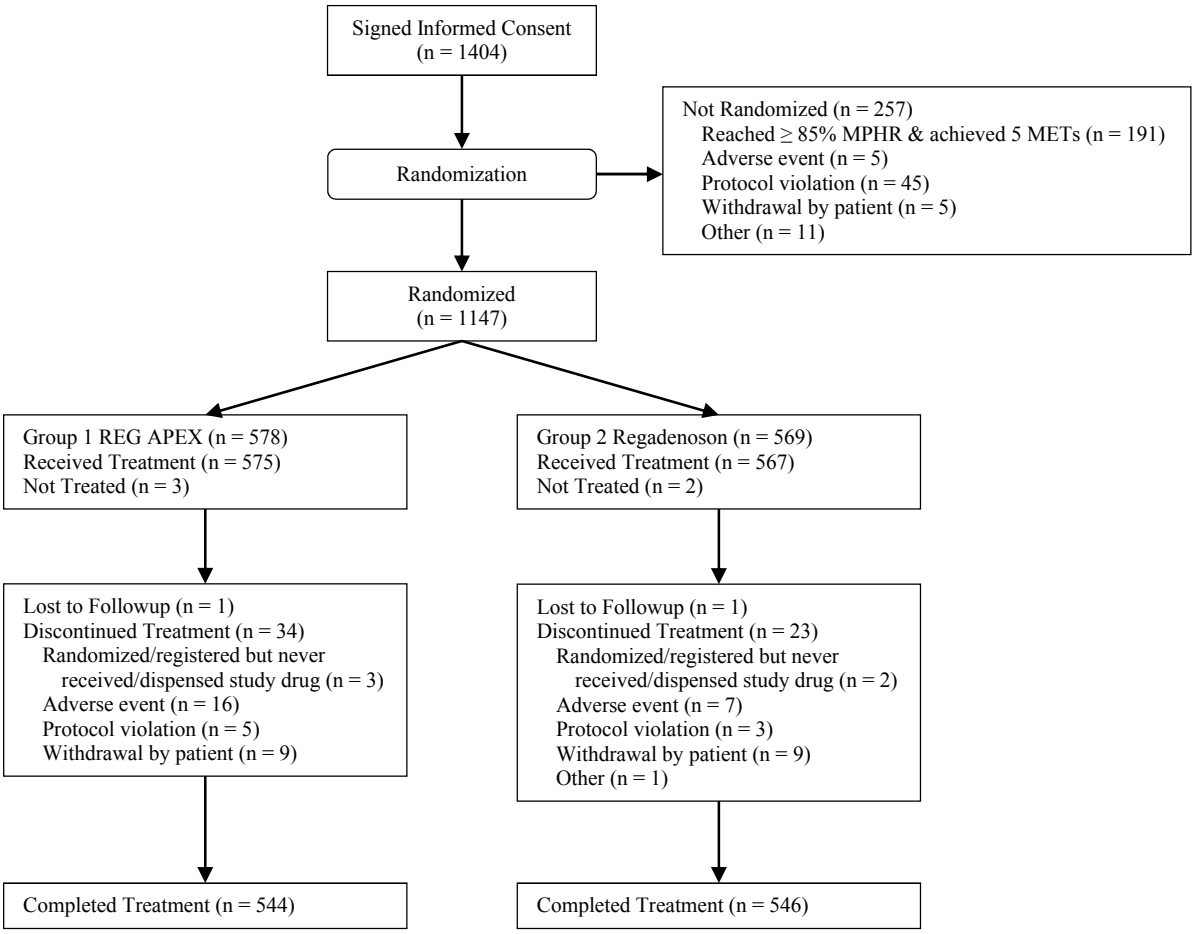
at visit 3 (MPI 2 [regadenoson alone]). In Group 2 (regadenoson), patients received regadenoson 1 hour after exercise recovery then underwent a stress SPECT MPI at visit 2 (MPI 1 [regadenoson alone]) and patients received regadenoson at rest without exercise then underwent a stress SPECT MPI at visit 3 (MPI 2 [regadenoson alone]).

Patients were administered open-label regadenoson 0.4 mg in a 5 mL intravenous bolus as a pharmacological stress agent prior to each stress SPECT procedure. A frequency of at least 24 hours was stipulated between each dose of regadenoson. Telephone follow-up was to occur 24 ± 4 hours and 30 days after the last dose of regadenoson to inquire for adverse events (AEs) and serious adverse events (SAEs), respectively.

Three independent expert readers were selected to review the SPECT cardiac scans in a blinded fashion, including blinding to all patient identifying information.

Number of Patients (Planned, Enrolled and Analyzed): The planned number of subjects was 1130. Of the 1404 patients screened for this study, 1147 patients were randomized: 578 patients in Group 1 (REG APEX) and 569 patients in Group 2 (regadenoson) [Figure 1].

Figure 1 Disposition of Patients



MET: metabolic equivalent; MPHR: maximum predicted heart rate; REG APEX: regadenoson after peak exercise

Source: Tables 12.1.1.1 and 12.1.1.3

A total of 1142 enrolled and randomized patients (575 patients in Group 1 [REG APEX] and 567 in Group 2 [regadenoson]) received at least 1 dose of regadenoson to be included in the Safety Analysis Set (SAF). Of the 1142 patients in the SAF, 1073 patients (538 patients in Group 1 [REG APEX] and 535 in Group 2 [regadenoson]) had interpretable SPECT scans at all visits as determined by at least 2 of the 3 blinded independent expert readers to be included in the Full Analysis Set [FAS]. Of the 1073 patients in the FAS, 1045 patients (518 patients in Group 1 [REG APEX] and 527 in Group 2 [regadenoson]), had no major protocol deviations to be included in the Per Protocol Set (PPS). Of all randomized patients, 31 patients (22 patients in Group 1 [REG APEX] and 9 in Group 2 [regadenoson]) had interpretable SPECT scans (rest and first stress) by at least 2 of the 3 blinded independent expert readers and interpretable invasive coronary angiography (ICA).

Diagnosis and Main Criteria for Inclusion: Patients that were eligible to participate in this study were ≥ 18 years of age and referred for an exercise or pharmacologic stress test SPECT MPI procedure for the evaluation of coronary artery disease (CAD). Patients referred for pharmacologic stress were to have had a reasonable potential of attempting exercise stress in the opinion of the investigator. Patient were to have had 1 of the following: past ischemia on any prior imaging stress test without invasive intervention on the artery subtending this territory; known CAD with symptoms similar to previous ischemic symptoms, recent onset of symptoms or recently worsened symptoms suggestive of ischemia; Diamond Forrester estimated pretest probability of CAD of ≥ 50%; history of most recent coronary artery bypass surgery or most recent percutaneous coronary intervention (PCI) > 10 years; or previously demonstrated 100% occlusion by invasive coronary or computed tomography (CT) angiography without successful intervening revascularization. A patient with CAD was to have had an intermediate to low risk for immediate intervention. Female patients were to use acceptable forms of birth control. Patients were to abstain from eating and drinking (3 hours prior to 30 minutes post study drug administration), consuming methylxanthine-containing foods and beverages (12 hours prior to administration of study drug) and dipyridamole or dipyridamole containing compounds or xanthine bronchodilators (aminophylline/theophylline) (48 hours prior to study drug administration).

Test Product, Dose and Mode of Administration, Batch Numbers: Lexiscan® (regadenoson) was administered as a single intravenous bolus injection of 0.4 mg in 5 mL over approximately 10 seconds. Resting SPECT imaging was performed in sequence prior to regadenoson stress SPECT imaging, regardless of randomization sequence. Packaging lot numbers [redacted] and [redacted] were used in the study.

Duration of Treatment: Patients were administered a single dose of regadenoson prior to each stress stress SPECT procedure. Each patient had 1 rest and 1 regadenoson stress procedure on visit 2 and had 1 regadenoson stress procedure on visit 3.

Criteria for Evaluation: The primary variable was the difference in agreement rates of both groups. Agreements were calculated by dividing the number of patients in the group where the majority of readers agree on their individual assessment of the absence or presence of ischemia (0 - 1 vs ≥ 2 defects reversible segments) for the 2 stress SPECT MPI scans with the total number patients in the group. The secondary variables were image agreement and image quality. SPECT scan agreement between imaging with regadenoson following inadequate exercise stress testing and imaging with regadenoson alone was analyzed by ischemia categories, reader's summed stress score (SSS) and summed difference score (SDS) and paired comparisons of ischemic extent. Image quality was evaluated by assessing the overall image quality, radiotracer ratios and radiotracer interference.

Safety and tolerability was assessed using the safety composite variable, treatment-emergent adverse events (TEAEs) (frequency, severity, seriousness and relationship to study drug regimen), clinical laboratory evaluations (hematology and biochemistry), vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP] and heart rate [HR]), physical examination, electrocardiograms (ECGs) (12-lead ECG and continuous 12-lead ECG), liver safety monitoring and assessment (AEs of possible hepatic origin and liver function tests [LFTs]) and radiotracer dose.

Statistical Methods: The primary assessment of the noninferiority hypothesis is provided by a CI on the difference in agreement rates (agreement rate for Group 1 [REG APEX] minus agreement rate for Group 2 [regadenoson]). The CI was calculated using the Newcombe score methodology. With each group assumed to have a majority agreement rate of 86% (based on the regadenoson pivotal studies data), the lower confidence bound of the 1-sided alpha level of 0.025 of the difference in agreement rates must have exceeded -0.075 in order to demonstrate noninferiority. The primary efficacy assessment was performed for the FAS population. A secondary analysis in the PPS and sensitivity analyses were also performed.

For ischemia categories, an assessment of noninferiority is provided by a CI on the difference in agreement rates (agreement rate for Group 1 [REG APEX] minus agreement rate for Group 2 [regadenoson]) for the 2 category (difference in must exceed -0.10 in order to demonstrate noninferiority) and 3 category (difference must exceed -0.133 in order to demonstrate noninferiority) variables for ischemia. For both SSS and SDS, agreement within each group (Group 1 [REG APEX]: agreement between exercise + REG and REG; Group 2 [regadenoson]: agreement between REG and REG) was assessed by Cohen's Kappa statistic and Cohen's weighted Kappa statistic. For the paired comparisons of ischemic extent, the median of the assessment of the 3 readers was calculated (-1 = less, 0 = the same, 1 = more). The count and percent of all image pairs in each category was summarized by group.

Image quality was analyzed using the median rating across the 3 readers with 1 = poor, 2 = fair, 3 = good and 4 = excellent. The radiotracer ratios are summarized descriptively by group by stress SPECT MPI. Radiotracer interference was analyzed using the median rating across the 3 readers.

Summary of Results/Conclusions:

Population: The mean age of patients included in the SAF was 61.9 years (range 28 to 90 years) Table 1. The population was primarily white (78.5%) and mostly male (58.6%). No significant differences were identified between the randomized treatment sequences in terms of any demographic characteristic. The demographic characteristics of the FAS and PPS were similar to those in the SAF.

Table 1 Demographics Characteristics

Parameter Category/Statistic	Group 1 REG APEX (n = 575)	Group 2 Regadenoson (n = 567)	Total (n = 1142)
Sex, n (%)			
Male	341 (59.3)	328 (57.8)	669 (58.6)
Female	234 (40.7)	239 (42.2)	473 (41.4)
Ethnicity, n (%)			
Hispanic or Latino	111 (19.3)	106 (18.7)	217 (19.0)
Not Hispanic or Latino	464 (80.7)	460 (81.1)	924 (80.9)
Missing	0	1 (0.2)	1 (0.1)
Race, n (%)			
White	456 (79.3)	441 (77.8)	897 (78.5)
Black or African American	71 (12.3)	83 (14.6)	154 (13.5)
Asian	42 (7.3)	37 (6.5)	79 (6.9)
American Indian or Alaska Native	0	3 (0.5)	3 (0.3)
Native Hawaiian or Other Pacific Islander	5 (0.9)	1 (0.2)	6 (0.5)
Other	1 (0.2)	2 (0.4)	3 (0.3)
Age, years			
Mean (SD)	61.9 (11.45)	61.9 (11.19)	61.9 (11.32)
Median	61.0	62.0	62.0
Min - Max	28 - 90	28 - 90	28 - 90
Age Group, years			
18 to 64	339 (59.0)	345 (60.8)	684 (59.9)
65 to 74	150 (26.1)	144 (25.4)	294 (25.7)
≥ 75	86 (15.0)	78 (13.8)	164 (14.4)
Weight (kg)			
Mean (SD)	89.35 (21.337)	88.77 (21.520)	89.07 (21.421)
Median	87.70	85.60	86.40
Min - Max	40.9 - 194.1	42.3 - 164.5	40.9 - 194.1
Height (cm)			
Mean (SD)	169.28 (10.380)	168.77 (9.902)	169.02 (10.144)
Median	170.18	169.00	170.18
Min - Max	121.9 - 193.0	144.8 - 195.6	121.9 - 195.6
BMI (kg/m^2)			
Mean (SD)	31.14 (6.812)	31.10 (6.826)	31.12 (6.816)
Median	30.21	29.74	30.02
Min - Max	14.4 - 61.4	15.4 - 56.7	14.4 - 61.4
Geographic Region, n (%)			
North America	563 (97.9)	558 (98.4)	1121 (98.2)
South America	12 (2.1)	9 (1.6)	21 (1.8)

All randomized patients who took at least 1 dose of study drug (Safety Analysis Set).
BMI: body mass index; Max: maximum; Min: minimum; REG APEX: regadenoson after peak exercise.
Source: Table 12.1.2.1.3

Efficacy Results: In the primary analysis of the primary efficacy variable, the lower bound for the 95% CI of the difference in agreement rates was greater than the noninferiority margin of -0.075 (agreement rate difference 95% CI: -0.06, -0.00), demonstrating that the agreement rate for Group 1 (REG APEX) where patients followed the exercise + regadenoson procedure for the first stress MPI is not inferior to the agreement rate for Group 2 (regadenoson) where patients received regadenoson alone for the first stress MPI [Table 2]. In the secondary analysis of the primary efficacy variable, noninferiority was also achieved in the PPS (agreement rate difference 95% CI: -0.06, 0.00). All exploratory analyses of the primary efficacy variable also achieved noninferiority

using different implementations for the handling of missing data as well as only including patients with interpretable scans at all visits as determined by all 3 readers.

Table 2 Majority Agreement between Stress MPI 1 and Stress MPI 2 Based on Ischemia Status Defined by Number of Reversible Defects

Agreement on Ischemic Status†	No	Yes	Agreement Rate (SE) (95% CI)	Agreement Rate Difference (SE) (95% CI)‡
Group 1 REG APEX				
Reader 1 Self-agreement (n = 524)	47 (9.0%)	477 (91.0%)		
Reader 2 Self-agreement (n = 536)	68 (12.7%)	468 (87.3%)	0.92 (0.012)	
Reader 3 Self-agreement (n = 537)	44 (8.2%)	493 (91.8%)	(0.89, 0.94)	
Majority Agreement (n = 538)§	44 (8.2%)	494 (91.8%)		-0.03 (0.015)
Group 2 Regadenoson				(-0.06, -0.00)
Reader 1 Self-agreement (n = 523)	36 (6.9%)	487 (93.1%)		
Reader 2 Self-agreement (n = 528)	48 (9.1%)	480 (90.9%)	0.95 (0.009)	
Reader 3 Self-agreement (n = 534)	33 (6.2%)	501 (93.8%)	(0.93, 0.97)	
Majority Agreement (n = 535)§	26 (4.9%)	509 (95.1%)		
Achieves Noninferiority Criteria (yes/no)	Yes			

All randomized patients with interpretable SPECT scans at all visits as determined by at least 2 of the 3 blinded independent expert readers (Full Analysis Set).

MPI: myocardial perfusion imaging; REG APEX: regadenoson after peak exercise; SPECT: single photon emission computed tomography

† Agreement between stress SPECT MPI 1 scan and stress SPECT MPI 2 scan on whether patient had ischemia present or absent.

‡ If the lower confidence bound of the 1-sided alpha level of 0.025 of the difference in agreement rates exceeded -0.075, noninferiority would be demonstrated.

§ Majority agreement categorized as yes if at least 2 of the 3 readers had self-agreement of yes.

Source: Table 12.3.1.1

For the analysis of image agreement using 2 ischemia categories, the difference (SE) between the 2 agreement rates is -0.01 (0.063) (95% CI: -0.14, 0.11), therefore, noninferiority is not demonstrated. Using 3 ischemia categories, the difference (SE) between the 2 agreement rates is -0.02 (0.027) (95% CI: -0.07, 0.04); noninferiority cannot be assessed because of insufficient data. Agreement rates based on reader SSS were similar between the groups, the difference between the 2 rates was 0.02 (0.022) (95% CI: -0.03, 0.06). In Group 1 (REG APEX), the agreement rate between stress MPI 1 and stress MPI 2 for SDS categories was 99.3% (534/538) with a weighted kappa estimate of 60%. In Group 2 (regadenoson), the agreement rate between stress MPI 1 and stress MPI 2 for SDS categories was 99.1% (530/535) with a weighted kappa estimate of 54%. For Group 1 (REG APEX) and Group 2 (regadenoson), stress MPI 1 scans were evaluated as showing less reversible defects more often than the MPI 2 scans when performing a paired comparison of ischemic extent.

For the analysis of image quality, the median rating of overall image quality across the 3 readers for the majority of the scans was good (range: 53.3% - 57.6% of scans) or excellent (range: 26.0% - 41.6% of scans) for the rest, stress MPI 1 and stress MPI 2 scans of both groups. The differences of radiotracer uptake ratios in Group 1 (REG APEX) between stress MPI 1 (exercise + regadenoson) and stress MPI 2 (regadenoson alone) were larger (range 0.100 to 0.150) than those in Group 2 (regadenoson) between the first (regadenoson alone) and second (regadenoson alone) MPI (range 0.000 to 0.050). The differences in Group 1 (REG APEX) were statistically significant (P value < 0.001). Approximately 70% of stress MPI 1 and stress MPI 2 scans in both

groups had slight subdiaphragmatic interference; and approximately 30% had moderate subdiaphragmatic interference. In Group 1 (REG APEX), the difference between stress MPI 1 (exercise + regadenoson) and MPI 2 (regadenoson alone) was statistically different (difference [SE]: -0.1 [0.04], P value = 0.019); however, the difference between Group 1 (REG APEX) and Group 2 (regadenoson) in MPI 1 was not significantly different (difference [SE]: -0.0 [0.04], P value = 0.333).

Safety Results: Overall, approximately 57% of patients experienced at least 1 TEAE at each stress MPI Table 3. The most common TEAEs were dyspnea, headache, dizziness and flushing for both stress MPI 1 and MPI 2 of both Group 1 (REG APEX) and Group 2 (regadenoson), which is consistent with the known safety profile of regadenoson.

Table 3 Incidence of Common TEAEs Occurring in ≥ 5% of Patients in Any Treatment Group

MedDRA v11.1 System Organ Class Preferred Term	Group 1 REG APEX		Group 2 Regadenoson	
	Stress MPI 1 Exercise + Regadenoson (n = 575)	**Stress MPI 2 Regadenoson Alone (n = 544)**	**Stress MPI 1 Regadenoson Alone (n = 567)**	**Stress MPI 2 Regadenoson Alone (n = 548)**
Any TEAE	**302 (52.5%)**	**317 (58.3%)**	**329 (58.0%)**	**323 (58.9%)**
Gastrointestinal Disorders				
Abdominal pain upper	31 (5.4%)	35 (6.4%)	35 (6.2%)	34 (6.2%)
Nausea	43 (7.5%)	44 (8.1%)	45 (7.9%)	41 (7.5%)
General Disorders and Administration Site Conditions				
Chest discomfort	37 (6.4%)	33 (6.1%)	54 (9.5%)	43 (7.8%)
Nervous System Disorders				
Dizziness	107 (18.6%)	75 (13.8%)	89 (15.7%)	81 (14.8%)
Dysgeusia	16 (2.8%)	27 (5.0%)	25 (4.4%)	23 (4.2%)
Headache	85 (14.8%)	108 (19.9%)	137 (24.2%)	118 (21.5%)
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnoea	141 (24.5%)	125 (23.0%)	161 (28.4%)	152 (27.7%)
Vascular Disorders				
Flushing	47 (8.2%)	78 (14.3%)	79 (13.9%)	69 (12.6%)

All randomized patients who took at least 1 dose of study drug (Safety Analysis Set).

A TEAE was defined as an adverse event observed from the time of administration of regadenoson to within 24 hours of administration of regadenoson for each stress MPI.

MPI: myocardial perfusion imaging; REG APEX: regadenoson after peak exercise; TEAE: treatment-emergent adverse event

Source: Tables 12.6.1.2.1 and 12.6.1.2.12

No deaths were reported in this study.

There were 9 patients who experienced 12 treatment-emergent SAEs in this study Table 4. During all of the stress MPIs, fewer than 1% of patients experienced SAEs. The SAEs were single occurrences, except for myocardial ischaemia (2 patients in Group 1 [REG APEX], 1 SAE during stress MPI 1 [exercise + regadenoson] and 1 SAE during stress MPI 2 [regadenoson alone]) and both were considered unrelated to treatment by the investigator. All of the SAEs either resolved or were resolving by the end of the study.

Table 4 Incidence of Serious TEAEs

MedDRA v11.1 System Organ Class Preferred Term	Group 1 REG APEX		Group 2 Regadenoson	
	Stress MPI 1 Exercise + Regadenoson (n = 575)	Stress MPI 2 Regadenoson Alone (n = 544)	Stress MPI 1 Regadenoson Alone (n = 567)	Stress MPI 2 Regadenoson Alone (n = 548)
Any Serious TEAE	**5 (0.9%)**	**2 (0.4%)**	**1 (0.2%)**	**1 (0.2%)**
Cardiac Disorders				
Acute coronary syndrome	1 (0.2%)	0	0	0
Cardiac failure congestive	0	0	1 (0.2%)	0
Myocardial infarction	1 (0.2%)	0	0	0
Myocardial ischaemia	1 (0.2%)	1 (0.2%)	0	0
Eye Disorders				
Vision blurred	1 (0.2%)	0	0	0
Gastrointestinal Disorders				
Pancreatitis	0	1 (0.2%)	0	0
Investigations				
Anticoagulation drug level below therapeutic	0	0	0	1 (0.2%)
Hepatic enzyme abnormal	1 (0.2%)	0	0	0
Nervous System Disorders				
Dizziness	1 (0.2%)	0	0	0
Speech disorder	1 (0.2%)	0	0	0
Syncope	1 (0.2%)	0	0	0

All randomized patients who took at least 1 dose of study drug (Safety Analysis Set).

A TEAE was defined as an adverse event observed from the time of administration of regadenoson to within 24 hours of administration of regadenoson for each stress MPI.

MPI: myocardial perfusion imaging; REG APEX: regadenoson after peak exercise; TEAE: treatment-emergent adverse event

Source: Table 12.6.1.6.1

The safety composite variable is comprised of treatment-emergent clinically significant cardiac events. Overall, 3% or fewer patients experienced a treatment-emergent clinically significant cardiac event Table 5. The only cardiac events experienced by more than 1 patient were ST-T depression (≥ 2 mm) and ST-T elevation (≥ 1 mm), with ST-T depression (≥ 2 mm) being the most common. This is also true when patients who had the same abnormality prior to study drug administration were excluded.

Table 5 Incidence of Treatment-emergent Clinically Significant Cardiac Events

Cardiac Event	Group 1 REG APEX		Group 2 Regadenoson	
	Stress MPI 1 Exercise + Regadenoson (n = 575)	Stress MPI 2 Regadenoson Alone (n = 544)	Stress MPI 1 Regadenoson Alone (n = 567)	Stress MPI 2 Regadenoson Alone (n = 548)
Any Cardiac Event	**17 (3.0%)**	**5 (0.9%)**	**3 (0.5%)**	**2 (0.4%)**
Any Holter/12-lead ECG Abnormality				
ST-T depression (≥ 2 mm)	13 (2.3%)	3 (0.6%)	2 (0.4%)	2 (0.4%)
ST-T elevation (≥ 1 mm)	3 (0.5%)	2 (0.4%)	1 (0.2%)	0
Any Adverse Event per SMQ for Myocardial Infarction (MedDRA v11.1)				
Acute coronary syndrome	1 (0.2%)	0	0	0
Myocardial infarction	1 (0.2%)	0	0	0

All randomized patients who took at least 1 dose of study drug (Safety Analysis Set).

A treatment-emergent Holter/12-lead ECG event is an event observed from the time of administration of regadenoson to within 1 hour after regadenoson administration.

A TEAE was defined as an adverse event observed from the time of administration of regadenoson to within 24 hours of administration of regadenoson for each stress MPI.

ECG: electrocardiogram; MPI: myocardial perfusion imaging; REG APEX: regadenoson after peak exercise; SMQ: standardized MedDRA query; TEAE: treatment-emergent adverse event

Source: Table 12.6.1.11.1.1

CONCLUSIONS: The primary efficacy analysis confirmed that the strength of agreement between SPECT imaging with regadenoson 3 minutes after inadequate exercise stress testing (in walk recovery [Group 1 (REG APEX)]) and SPECT imaging with regadenoson without exercise (Group 2 [regadenoson]) was not inferior to the strength of agreement between 2 sequential SPECT imaging scans with regadenoson without exercise. A similar finding was confirmed in the PPS secondary and exploratory analyses where missing data was handled differently and included only patients with scans interpreted by all 3 readers at all visits.

The secondary analysis of agreement rates with respect to 3 categories for ischemia (0 – 1, 2 – 4 and ≥ 5 median number of reversible defects) could not be assessed for noninferiority because of insufficient data. Noninferiority was not demonstrated for the agreement rate with respect to 2 categories of ischemia (0 - 1 and ≥ 2 median number of reversible defects). SSS, SDS and side-by-side comparisons for ischemic extent were similar for Group 1 (REG APEX) and Group 2 (regadenoson).

The image quality of the first stress MPI scan and the second stress MPI scan was comparable in both Group 1 (REG APEX) and Group 2 (regadenoson). The overall image quality across the 3 readers for the majority of the scans was good or excellent; overall image quality was not significantly affected by exercise duration. Approximately 70% of stress MPI 1 and stress MPI 2 scans in both groups had slight subdiaphragmatic interference and approximately 30% had moderate subdiaphragmatic interference, with segments 4 and 10 being the most commonly obscured.

Results of the exploratory efficacy variables also support the comparability of the exercise + regadenoson MPI and the regadenoson alone MPI. Of the less than 20% of patients with wall motion abnormalities in each group, 101/533 (18.9%) in Group 1 (REG APEX) and 84/534 (15.7%) in Group 2 (regadenoson) showed that the severity of the abnormalities was similar in both stress MPI 1 and stress MPI 2 scan images. Due to the small sample size, the agreement rate, sensitivity and specificity of ICA and regadenoson stress MPI results for Group 1 (REG APEX) and Group 2 (regadenoson) may not be meaningful. In regards to diagnostic certainty, stress MPI 1 and stress MPI 2 gave similar results for overall findings for both Group 1 (REG APEX) and Group 2

(regadenoson), with the largest percentage of patients for both scans in both groups rated as definitely normal, which was confirmed when the diagnostic certainty assessments were collapsed into 2 outcomes.

As was observed with the regadenoson alone scan (stress MPI 2), the majority of patients had no apparent transient ischemic dilation following the stress MPI 1 scan. When the image quality of the stress MPI 1 scan and stress MPI 2 were compared side-by-side, the stress MPI 1 image quality was considered the same or better than the stress MPI 2 image quality in more than 80% of the patients for both groups.

More than 85% of patients in both groups rated the comfort of stress MPI 1 as "comfortable" or "a little uncomfortable." When patients in Group 1 (REG APEX) and Group 2 (regadenoson) were asked "How did the first test at visit 2 compare to the stress test performed today (stress MPI 2)?," 28.8% and 21.5% of patients, respectively, responded with "much better" and 15.9% and 18.8% of patients, respectively, responded with "somewhat better."

The primary secondary variable was the safety composite variable defined as the percentage of patients who experienced at least 1 treatment-emergent clinically significant cardiac event. Overall, 3% or fewer patients at any stress MPI experienced a treatment-emergent clinically significant cardiac event. While the number of patients experiencing these events is numerically greater for the exercise + regadenoson stress MPI (Group 1 [REG APEX] MPI 1) than for the regadenoson alone stress MPIs (Group 1 [REG APEX] MPI 2 and Group 2 [regadenoson]), it is difficult to draw conclusions due to the low incidence of all treatment-emergent clinically significant cardiac events. ST changes were the most common clinically significant cardiac events, an increased incidence of ST changes was anticipated in patients who received pharmacological stress (regadenoson) shortly after exercise stress.

Overall, approximately 57% of patients experienced at least 1 TEAE at each stress MPI and most were considered drug related. The most common TEAEs were dyspnea, headache, dizziness and flushing, which is consistent with the known safety profile of regadenoson. Most TEAEs were mild or moderate in severity.

No deaths were reported in this study. There were 9 patients who experienced 12 treatment-emergent SAEs in this study. All of the SAEs either resolved or were resolving by the end of the study. There were 19 patients who experienced 30 SAEs that had an onset of more than 24 hours after regadenoson administration in this study. All of these SAEs were considered not related to study drug.

Three patients experienced cardiovascular events of interest; 2 patients in Group 1 (REG APEX) MPI 1 after receiving regadenoson (acute coronary syndrome and myocardial infarction) and 1 patient in screening during exercise testing (ST segment elevation, angina and bradycardia).

There were 19 patients who experienced 20 TEAEs leading to permanent discontinuation in this study. Fifteen TEAEs leading to permanent discontinuation of study drug were considered possibly or probably related.

In patients from Group 1 (REG APEX) MPI 1, 29.2% had a decrease in SBP of > 35 mm Hg, while 6.3% to 9.5% of patients in either Group 1 (REG APEX) MPI 2 or Group 2 (regadenoson) experienced this decrease while undergoing a regadenoson alone stress MPI when using baseline as last observation prior to study drug administration (and during the walk recovery). When baseline was defined as the last observation immediately prior to exercise, the incidence of patients experiencing a decrease in SBP of > 35 mm Hg while undergoing an exercise + regadenoson stress MPI dropped to 8.0%, within the range seen in patients undergoing the regadenoson alone stress MPI. Fewer than 1% of patients had a TEAE of hypotension.

Patients in Group 1 (REG APEX) MPI 1, 43.6% of patients had a pulse rate > 100 bpm, while 23.8% to 30.6% of patients experienced this increase while undergoing a regadenoson alone stress MPI.

Of the patients in Group 1 (REG APEX) MPI 1, 83.1% had an abnormal 12-lead ECG result as assessed by central review at any time point post dose, and 68.8% to 75.0% of patients who underwent a regadenoson alone stress MPI had an abnormal ECG result.

Five patients met the ECG criteria of ST segment elevation (≥ 1 mm) post regadenoson administration. Four in Group 1 (REG APEX), of which 2 patients had ST segment elevation on MPI 1 only, 1 patient had ST segment elevation on both MPI 1 and MPI 2 and 1 patient had ST segment elevation on MPI 2 only. The patient in Group 2 (regadenoson) had ST segment elevation on MPI 1 only.

Eleven patients in Group 1 (REG APEX) met the ECG criteria of ST depression ≥ 2 mm post regadenoson administration during MPI 1 only; of these, 9 patients underwent the second MPI. Of these 11 patients, 2 patients met the criteria during walk recovery and also following regadenoson administration. Two patients had normal ECGs prior to exercise and met ECG criteria of ST depression at a single time point after the administration of regadenoson. Seven patients had ST depression on the pre-exercise ECG or developed ST depression during exercise or walk recovery, but met the criteria of ST depression ≥ 2 mm after regadenoson administration. In general, ECGs changes were transient and had returned to baseline within 60 minutes. Three patients in Group 2 (regadenoson) experienced ST depression post regadenoson administration that met the criteria for clinical significance.

Approximate mean total radiation dose received in both groups was 18.5 mSv total.

In conclusion:

- The strength of agreement between SPECT imaging with regadenoson 3 minutes after inadequate exercise stress testing (in walk recovery) and SPECT imaging with regadenoson without exercise is not inferior to the strength of agreement between 2 sequential SPECT imaging scans with regadenoson without exercise.
- Overall image quality for the majority of scans was good or excellent.
- The heart:liver/gut ratios were more favorable in Group 1 (REG APEX) with a range of 0.100 to 0.150 than those in Group 2 (regadenoson) with a range of 0.000 to 0.050.
- The number of patients experiencing at least 1 treatment-emergent clinically significant cardiac event in SPECT imaging 3 minutes after inadequate exercise stress testing (in walk recovery) plus regadenoson is 3% and in SPECT imaging with regadenoson without exercise ranged from 0.4% to 0.9%.
- Regadenoson was generally safe and well tolerated with or without association with exercise.

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