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

SYNOPSIS

Title of Study: A Phase 3b, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Effect of Caffeine Intake on Single Photon Emission Computed Tomography (SPECT) Myocardial Perfusion Imaging (MPI) in Subjects Administered Regadenoson (3606-CL-3002)

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

Study Center(s): This phase 3b, multicenter study was initiated at 29 sites in the United States (US) with 24 of the sites enrolling subjects.

Publications (references): None

Study Period: 1.25 years

Date of first enrollment (Study initiation date): March 24, 2009

Date of last evaluation (Study completion date): July 15, 2010

Phase of Development: 3b

Objectives: The primary objective of the study was to determine whether oral administration of 200 mg or 400 mg caffeine adversely compromised diagnostic accuracy of detecting reversible defects in adult subjects with a known likelihood of coronary artery disease (CAD) undergoing single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) with regadenoson.

The secondary objective of the study was to evaluate the exposure-response relationship between regadenoson exposure and pharmacodynamic effects including heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP). The effect of caffeine and its metabolites, paraxanthine and theobromine, on regadenoson exposure-response relationship was explored.

The safety of concomitant administration of caffeine and regadenoson in this population was also assessed.

Methodology: This was a multicenter, randomized, double-blind, placebo-controlled, parallel group study in subjects with CAD administered regadenoson undergoing a subsequent SPECT MPI. After successful screening, subjects completed a rest SPECT MPI on day 1 (MPI 1). Eligible subjects then returned on day 3 for randomization into one of three treatment arms (1:1:1): caffeine 200 mg plus regadenoson, caffeine 400 mg plus

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

regadenoson and placebo plus regadenoson. Randomized subjects were administered an intravenous bolus injection of 0.4 mg regadenoson per 5 mL and completed an initial stress SPECT MPI (MPI 2). Subjects with ≥ 1 reversible defect(s) (based on the investigator interpretation) continued to the double-blind treatment period. If there was only 1 reversible defect and the defect was in segment 17, another reversible defect needed to be present for the subject to continue to the double-blind treatment period. On day 5, after fasting for at least 4 hours, subjects were administered oral caffeine (200 mg or 400 mg) or placebo capsules in a blinded fashion. Ninety minutes after administration of the caffeine or placebo capsules, subjects were administered an intravenous bolus injection of 0.4 mg regadenoson per 5 mL and completed a second stress SPECT MPI (MPI 3). Subjects returned for a final follow-up visit (day 6) at least 24 hours after their last SPECT MPI for safety assessments.

Number of Subjects (planned, enrolled and analyzed): Approximately 360 subjects were to be randomized in the study (approximately 120 in each treatment arm). There were 347 subjects randomized into the study: 116 subjects in the caffeine 200 mg plus regadenoson group, 117 subjects in the caffeine 400 mg plus regadenoson group and 114 subjects in the placebo plus regadenoson group.

Of the 347 subjects randomized, 345 (99.4%) were in the safety analysis set (SAF), 207 (59.7%) were in the full analysis set (FAS), 200 (57.6%) were in the per protocol set (PPS) and 207 (59.7%) were in the pharmacokinetic set (PKAS). The number and percentages of subjects in each treatment group for these analysis sets are presented in [Table 1].

Diagnosis and Main Criteria for Inclusion: Male or female subjects, at least 18 years-of-age, with ≥ 1 reversible defect(s) (if there was only 1 reversible defect and the defect was in segment 17, another reversible defect needed to be present) and at least a 50% likelihood of CAD as determined by the investigator using the Diamond & Forrester Categorization. Subjects also must ingest caffeinated food or beverages regularly (at least the equivalent of one cup of caffeinated coffee daily).

Test Product, Dose and Mode of Administration, Batch Numbers: Regadenoson 0.4 mg/5 mL (0.08 mg/mL), intravenous bolus injection (Lot Number [redacted]) over 10 seconds immediately followed by a 0.9% sodium chloride USP (saline) flush 5 mL, intravenously.

Caffeine 200 mg over-encapsulated capsules (Lot Number [redacted]) and over-encapsulated placebo-to-match caffeine were administered orally with 180 mL (6 oz) of water. Two placebo, 1 placebo and 1 200 mg caffeine capsule or 2 caffeine capsules (200 mg) were administered orally for a caffeine dose of 0, 200 or 400 mg, respectively.

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

Duration of Treatment (or Duration of Study, if applicable): Regadenoson administered on day 3 and day 5. Caffeine and/or placebo capsules administered on day 5.

Reference Product, Dose and Mode of Administration, Batch Numbers: Over-encapsulated placebo-to-match caffeine capsules (Lot Number [redacted]).

Criteria for Evaluation:

Efficacy: The primary efficacy variable was the change in number of reversible defects. The number of reversible ischemic defects was counted to determine if there was a change in the number of reversible defects present between MPI 2 and MPI 3. Segments were counted as having a reversible defect if the stress score was greater than the rest score and the stress score was ≥ 2. Scoring involved points assigned to each segment in direct proportion to the perceived count density of the segment based on a 5-point scale for radiopharmaceutical uptake, where 0 = normal radiotracer uptake and 4 = absent radiotracer uptake.

Secondary variables included the change in summed difference score (SDS), defined as the regadenoson with caffeine/placebo stress scan (MPI 3) SDS minus the regadenoson only stress scan (MPI 2) SDS and change in perfusion abnormality assessed by computerized quantitation. The Summed Stress Score (SSS) was calculated as the sum of the stress scores across the 17 segments. The Summed Rest Score (SRS) was calculated as the sum of the rest scores across the 17 segments. The SDS was calculated as the difference in the SSS and SRS (SSS – SRS).

Pharmacokinetics: Plasma concentrations were determined for regadenoson and for caffeine and its metabolites paraxanthine and theobromine. The pharmacokinetic analyses were performed using concentration data from samples collected on day 5 by model-independent, non-compartmental methods using WinNonlin version 5.3. The primary pharmacokinetic parameters for regadenoson were: AUC_{last}, $t_{1/2}$, CL_{tot} and V_{ss}. The primary pharmacokinetic parameters for caffeine and its metabolites, paraxanthine and theobromine were the same as the pharmacokinetic parameters for regadenoson if applicable (except the AUC_{last} occurs at 180 min) plus the addition of C_{min}, C_{max}, t_{max}.

Safety: Safety variables included adverse events (AEs), clinical laboratory evaluations, vital signs, physical examination and 12-lead electrocardiograms (ECGs).

Statistical Methods:

All statistical comparisons were made using two sided tests at the alpha = 0.05 significance level unless specifically stated otherwise. The following analysis sets were used for the analyses:

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

- Safety analysis set (SAF): All randomized subjects who received at least one dose of regadenoson. This population was used for safety analyses.
- Full analysis set (FAS): The FAS was defined as all randomized subjects with interpretable MPI 1, MPI 2 and MPI 3 scans as determined by 2 of the 3 blinded readers. All efficacy analyses were performed using this set unless specified otherwise.
- Per protocol set (PPS): The PPS was defined as the subset of the FAS with no major protocol deviations, using criteria defined by the medical monitor. Classification of subjects was determined before the blind was broken.
- Pharmacokinetic analysis set (PKAS): All subjects who provided adequate pharmacokinetic samples, as defined by the pharmacokineticist, to calculate the primary pharmacokinetic parameters were included in the PKAS. Subjects with missed doses or with other protocol violations were assessed on a subject-by-subject basis for inclusion in the PKAS. The PKAS was the primary set for all pharmacokinetic analyses.

Efficacy: The number of reversible defects as assessed by the central lab was the primary variable and the change in number of reversible defects between MPI 2 and MPI 3 was the primary endpoint for the study. The change in number of reversible defects was modeled using an analysis of covariance (ANCOVA) with treatment arm as a factor and the number of reversible defects at the initial stress scan (MPI 2) as a covariate. This was considered the primary analysis. Fisher's least significant difference (LSD) was used to test for an overall treatment arm effect using a Type 1 error rate of 5%. All pairwise comparisons were used to assess which treatment arm(s) was/were statistically different if the overall test for arm effect was significant.

As a secondary analysis, the primary analysis was repeated using only subjects having ≥ 1 reversible defect(s) (if the only defect was present in segment 17, at least one other reversible defect must have been evident) at MPI 2. As another secondary analysis, the primary analysis was repeated using the PPS. As a sensitivity analysis, a nonparametric ANCOVA, where the change in number of reversible defects and the number of reversible defects from MPI 2 were converted to ranks, was used to analyze the primary endpoint. The ranked change in number of reversible defects served as the response in an ANCOVA model with treatment arm as a factor and the ranked number of reversible defects from MPI 2 as a covariate.

The analysis of agreement of MPI 2 and MPI 3 with respect to ischemia size category (0 - < 2, 2 - < 5 or ≥ 5 segments with reversible defects) was performed between treatment arms

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

placebo and caffeine 200 mg, placebo and caffeine 400 mg, separately. The median count across the three independent readers was used for this analysis. Agreement rate and 95% Clopper-Pearson CI was calculated for each ischemia size category within treatment arm. The difference in the agreement rate between the treatment arms and associated 95% CI was also calculated for each ischemia size category. Test of marginal homogeneity was performed for each treatment arm separately, using SAS procedure CATMOD. Cochran-Mantel-Haenszel test of equality of mean scores between MPI 2 and MPI 3, as implemented in SAS procedure FREQ, was performed, using the following scoring system: 0 - < 2 = 0, 2 - < 5 = 1 and ≥ 5 = 2. To assess a possible increase in variability due to caffeine, the variability of the change in number of reversible defects for the 200 mg and 400 mg caffeine arms was compared to the placebo arm. Levene's test was performed with a Type 1 error rate of 5% to test for an increase in the variance of each caffeine arm relative to placebo if the variance of a caffeine group was greater than the placebo group. Multiplicity adjustments were not performed.

The change in SDS across all 17 segments and perfusion abnormality assessed by quantitation was analyzed using the same methods as the primary analysis with the corresponding variable at the initial stress scan used as a covariate.

Pharmacokinetics: The preliminary pharmacokinetic analyses were performed by model-independent, non-compartmental methods using WinNonlin version 5.3. Plasma concentrations of regadenoson, caffeine and its metabolites, paraxanthine and theobromine, were tabulated for each subject and summary statistics were computed for each sampling time. Descriptive statistics including the number of subjects (n), mean, SD, geometric mean, coefficient of variation (%CV), minimum, median and maximum values were provided for pharmacokinetic parameters.

Safety: All reported AEs were coded with system organ class (SOC) and preferred term using MedDRA V11.1. The treatment-emergent AEs (TEAEs) were tabulated by treatment group and SOC. The incidence of TEAE by severity and incidence of drug related TEAEs were also displayed. In addition, incidence of TEAEs leading to discontinuation of study medication and incidence of serious AEs (SAEs) were tabulated. TEAEs were those with onset date and time on or after the start of regadenoson and no more than 24 hours after the last dose of study medication. SAEs occurring within 30 days after the last dose of subject's study medication were included in summary tables for SAEs. All AEs and SAEs were listed for individual subjects, along with information regarding onset, duration, severity and relationship to regadenoson and caffeine.

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

Clinical laboratory data (cardiac markers, hematology and chemistry) and change from baseline were summarized by treatment group. Shift tables from baseline to each time point during treatment period in laboratory tests were also provided. Frequency tables were provided for ALT (alanine aminotransferase) and AST (alanine aminotransferase) with > 2 x upper limit of normal (ULN), 3 x ULN and 5 x ULN values and for bilirubin and serum creatinine with > 1.5 x ULN and 3 x ULN values. Laboratory measurements at each visit were listed for all subjects.

Changes in vital signs from baseline to each post-baseline time point were summarized by treatment group using descriptive statistics. Physical examination findings at baseline and follow-up visit and changes from baseline were presented by treatment group. Twelve-lead ECG data were collected at screening, MPI 1, MPI 2 and MPI 3. The number and percent of subjects with normal, not clinically significant abnormal and clinically significant abnormal results were tabulated by treatment group at each time point. Shift tables from MPI 2 ECG findings to MPI 3 ECG findings were generated for each treatment group.

Changes from planned analyses: There were no additions to the analyses described in the final SAP. In cases where the number of reversible defects scores were to be imputed, no imputation was used for missing defects. There was one pharmacokinetic parameter which was not produced as part of the final data listings and tables. The final SAP indicates that the paraxanthine-caffeine ratio and theobromine-caffeine ratio would be provided however these were not done during analysis.

Summary of Results/Conclusions:

Population: The number and percentage of subjects in each of the analysis sets is presented in [Table 1].

The study was completed by 57.9% of subjects in the placebo plus regadenoson group, 61.2% of subjects in the caffeine 200 mg plus regadenoson group and 61.5% of subjects in the caffeine 400 mg plus regadenoson group [Table 2].

The demographic and baseline characteristics were generally consistent between the placebo plus regadenoson and caffeine plus regadenoson groups and no significant differences were observed between the 3 groups in the demographics or baseline characteristics. The majority of the study population was male (79.2%), White (92.8%) and non-Hispanic or Latino (90.3%), with a mean of 67.7 years (range 32 to 91 years).

Efficacy Results: In the primary analysis, the mean number of reversible defects from MPI 2 to MPI 3 in the caffeine 200 mg plus regadenoson and caffeine 400 mg plus regadenoson

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

groups decreased while the mean number of reversible defects from MPI 2 to MPI 3 in the placebo plus regadenoson group increased. This change was significantly different than the changes observed in both the caffeine 200 mg plus regadenoson and caffeine 400 mg plus regadenoson groups [Table 4]. Results from analyses with subjects having ≥ 1 reversible defect and using a nonparametric ANCOVA analysis were similar.

The mean SDS from MPI 2 to MPI 3 in the caffeine 200 mg plus regadenoson and caffeine 400 mg plus regadenoson groups decreased while the mean SDS from MPI 2 to MPI 3 in the placebo plus regadenoson group increased and this change was significantly different than the change observed in both the caffeine 200 mg plus regadenoson and caffeine 400 mg plus regadenoson groups. In the caffeine 200 mg plus regadenoson and caffeine 400 mg plus regadenoson groups, the MPI 2 rates were statistically significantly different than the MPI 3 rates. In contrast, no significant differences were observed between MPI 2 and MPI 3 rates in the placebo plus regadenoson group.

All computerized quantitation results were similar to results assessed by blinded readers.

Pharmacokinetic Results: There was no apparent effect of caffeine on regadenoson plasma concentrations, as mean regadenoson concentrations were similar between treatment groups [Table 5]. Mean regadenoson CL_{tot} values were slightly lower in the caffeine 200 mg plus regadenoson and caffeine 400 mg plus regadenoson groups compared to the placebo plus regadenoson group. Mean regadenoson $t_{1/2}$ values were slightly higher in the caffeine 200 mg plus regadenoson and caffeine 400 mg plus regadenoson groups compared to the placebo plus regadenoson group. Caffeine did not appear to have an effect on regadenoson C_{max}, t_{max}, AUC_{last} and V_{ss} values [Table 6].

Mean caffeine and paraxanthine concentrations were higher in the caffeine 400 mg plus regadenoson treatment group compared to the caffeine 200 mg plus regadenoson group, while mean theobromine concentration levels were similar between the caffeine 400 mg plus regadenoson and the caffeine 200 mg plus regadenoson groups.

Safety Results: Overall, 77.9% of placebo plus regadenoson subjects, 79.3% of caffeine 200 mg plus regadenoson subjects and 75.0% of caffeine 400 mg plus regadenoson subjects reported at least 1 AE. Seventy-seven percent (77.0%) of placebo plus regadenoson subjects, 78.4% of caffeine 200 mg plus regadenoson subjects and 72.4% of caffeine 400 mg plus regadenoson subjects experienced regadenoson-related TEAEs, while 5.3% of placebo plus regadenoson subjects, 6.1% of caffeine 200 mg plus regadenoson subjects and 6.1% of caffeine 400 mg plus regadenoson subjects experienced caffeine related TEAEs. A summary of TEAEs occurring in > 5% of subjects is presented in [Table 7]. The most commonly

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

experienced AE of dyspnea was experienced by a smaller percentage of subjects in the caffeine 400 mg plus regadenoson group, than in the placebo plus regadenoson and caffeine 200 mg plus regadenoson groups. A greater percentage of subjects in the placebo plus regadenoson group experienced chest pain than the caffeine 200 mg plus regadenoson and caffeine 400 mg plus regadenoson groups. There was no decrease in the percentage of subjects who experienced headache in the two groups that received caffeine plus regadenoson compared with the group that received placebo plus regadenoson.

There were no deaths in this study. Five subjects experienced SAEs within the 30 day reporting window for SAEs. Only one of these subjects (caffeine 200 mg plus regadenoson group) reported a treatment emergent SAE of angina pectoris which was considered by the investigator to not have a relationship to regadenoson or caffeine. The other 4 subjects experienced SAEs that were not treatment-emergent including myocardial infarction; acute coronary syndrome; acute myocardial infarction and acute renal failure; and angina pectoris. In all cases these were not considered related to study drug. Four subjects discontinued due to AEs; 1 subject from the caffeine 200 mg plus regadenoson group discontinued due to a regadenoson-related AE.

There were no clinically important differences between the treatment groups with regard to clinical laboratory results, vital signs and ECG abnormalities.

CONCLUSIONS:

- Caffeine adversely compromised the diagnostic accuracy of detecting ischemic reversible defects in adult subjects with a known likelihood of CAD undergoing SPECT MPI with regadenoson. For all efficacy endpoints, there was a statistically significant difference between the placebo and caffeine treatment groups.
- There was no statistical difference between using caffeine 200 mg and caffeine 400 mg with regadenoson in detecting ischemic reversible defects.
- The overall incidence of TEAEs and of drug-related TEAEs was similar between all treatment groups.

Date of Report: March 1, 2011

Table 1 Summary of Analysis Sets

Analysis Set, n (%)	Placebo + Regadenoson (n = 114)	Caffeine 200 mg + Regadenoson (n = 116)	Caffeine 400 mg + Regadenoson (n = 117)
Full Analysis Set †	66 (57.9%)	70 (60.3%)	71 (60.7%)
Per Protocol Set ‡	64 (56.1%)	66 (56.9%)	70 (59.8%)
Safety Analysis Set §	113 (99.1%)	116 (100.0%)	116 (99.1%)
Pharmacokinetic Set ¶	66 (57.9%)	71 (61.2%)	70 (59.8%)

MPI: myocardial perfusion imaging.

† All randomized subjects with interpretable MPI 1, MPI 2 and MPI 3 scans.

‡ The subset of the full analysis set with no major protocol deviations.

§ All randomized subjects who received at least one dose of regadenoson.

¶ All subjects who provided adequate pharmacokinetic samples, as defined by the pharmacokineticist, to calculate the primary pharmacokinetic parameters.

Source: Table 12.1.1.1

Table 2 Subject Disposition - End of Treatment: All Randomized Subjects

Completed Study/ Reasons for Discontinuation, n (%)	Placebo + Regadenoson (n = 114)	Caffeine 200 mg + Regadenoson (n = 116)	Caffeine 400 mg + Regadenoson (n = 117)
Completed treatment			
No	48 (42.1%)	45 (38.8%)	45 (38.5%)
Yes	66 (57.9%)	71 (61.2%)	72 (61.5%)
Reasons for discontinuation			
Randomized but drug not received	1 (0.9%)	0	1 (0.9%)
AE	1 (0.9%)	3 (2.6%)	0
Withdrew consent (not related to AE)	0	0	0
Protocol violation	0	0	0
Lost to follow-up	0	1 (0.9%)	0
Sponsor discontinued subject or study	1 (0.9%)	0	0
Reversible ischemic defect not present	43 (37.7%)	40 (34.5%)	44 (37.6%)
Other	2 (1.8%)	1 (0.9%)	0
AE resulted in death †			
No	1 (0.9%)	3 (2.6%)	0
Yes	0	0	0

AE: adverse event.

† AEs leading to discontinuation.

Source: Table 12.1.1.2

Table 3 Summary of Subject Demographics and Other Baseline Characteristics

Parameter	Placebo + Regadenoson (n = 66)	Caffeine 200 mg + Regadenoson (n = 70)	Caffeine 400 mg + Regadenoson (n = 71)	Total (n =207)	P-value †
Sex, n (%)					0.1842
Male	55 (83.3%)	58 (82.9%)	51 (71.8%)	164 (79.2%)	
Female	11 (16.7%)	12 (17.1%)	20 (28.2%)	43 (20.8%)	
Ethnicity, n (%)					0.8753
Non-Hispanic or Latino	60 (90.9%)	64 (91.4%)	63 (88.7%)	187 (90.3%)	
Hispanic or Latino	6 (9.1%)	6 (8.6%)	8 (11.3%)	20 (9.7%)	
Race, n (%)					0.7030
White	61 (92.4%)	63 (90.0%)	68 (95.8%)	192 (92.8%)	
Black or African American	5 (7.6%)	5 (7.1%)	3 (4.2%)	13 (6.3%)	
American Indian or Alaska Native	0	1 (1.4%)	0	1 (0.5%)	
Native Hawaiian or other Pacific Islander	0	1 (1.4%)	0	1 (0.5%)	
Age, (years) n	66	70	71	207	0.0858
Mean (SD)	68.0 (9.99)	65.7 (11.11)	69.4 (8.23)	67.7 (9.91)	
Median	67.5	66.5	69.0	68.0	
Min, Max	43, 91	32, 86	46, 86	32, 91	
Height, (cm) n	66	69	71	206	0.3253
Mean (SD)	174.7 (9.08)	173.1 (9.81)	172.3 (8.57)	173.3 (9.17)	
Median	176.1	172.7	172.7	173.0	
Min, Max	147, 198	155, 196	150, 193	147, 198	
Weight, (kg) n	66	69	71	206	0.3153
Mean (SD)	99.17 (22.797)	98.42 (23.068)	93.96 (19.421)	97.12 (21.805)	
Median	97.07	93.89	89.36	93.21	
Min, Max	51.7, 180.5	63.5, 173.7	59.0, 154.2	51.7, 180.5	

The FAS included all randomized subjects with interpretable MPI 1, MPI 2 and MPI 3 scans.

ANOVA: analysis of variance; FAS: full analysis set; Min: minimum; Max: maximum; MPI: myocardial perfusion imaging.

P-value for a discrete variable is from a Fisher's Exact Test (2-tailed).

P-value for a continuous variable is from a one-way ANOVA.

Source: Table 12.1.2.1

Table 4 Mean Number of Reversible Defects and Mean Change in Number of Reversible Defects Between MPI 2 and MPI 3 (As Assessed By Blinded Readers)

Visit	Placebo + Regadenoson (n =66) Mean (SD)	Caffeine 200 mg + Regadenoson (n = 70) Mean (SD)	Caffeine 400 mg + Regadenoson (n = 71) Mean (SD)	Overall Treatment Effect P-value †
MPI 2	0.67 (1.377)	1.01 (1.452)	1.00 (1.595)	
MPI 3	0.80 (1.511)	0.40 (0.907)	0.38 (0.962)	
MPI 3- MPI 2	0.12 (0.981)	-0.61 (1.097)	-0.62 (1.367)	<0.001
P value vs. Placebo ‡		<0.001	<0.001	
P value vs. Caffeine 200 mg ‡			0.9328	

The FAS included all randomized subjects with interpretable MPI 1, MPI 2, MPI 3 scans.

ANCOVA: analysis of covariance; FAS: full analysis set; MPI: myocardial perfusion imaging.

† P-value is from the primary analysis using ANCOVA.

‡ The unadjusted P-values for pairwise differences should be used for interpretation only if the treatment effect's P-value ≤ 0.05.

Source: Table 12.3.1.1

Table 5 Day 5 (MPI 3) Mean Regadenoson Concentrations

Treatment Group Parameter	n	Mean (ng/mL)	SD	Min (ng/mL)	Median (ng/mL)	Max (ng/mL)	Geometric mean (ng/mL)
Placebo + Regadenoson							
3 minutes post-regadenoson dose	64	20.595	7.7541	7.24	19.235	50.03	19.296
30 minutes post-regadenoson dose	65	6.009	6.6578	2.25	4.500	52.26	4.876
60 minutes post-regadenoson dose	64	3.575	2.6687	1.29	2.865	19.44	3.080
120 minutes post-regadenoson dose	65	2.091	0.9671	0.85	1.890	5.55	1.913
Caffeine 200 mg + Regadenoson							
3 minutes post-regadenoson dose	70	20.978	6.9127	8.38	20.755	38.07	19.829
30 minutes post-regadenoson dose	71	5.269	2.6028	2.49	4.700	22.14	4.902
60 minutes post-regadenoson dose	71	3.484	1.9490	1.52	3.070	16.07	3.196
120 minutes post-regadenoson dose	71	2.432	1.8697	0.75	2.050	15.09	2.129
Caffeine 400 mg + Regadenoson							
3 minutes post-regadenoson dose	69	19.660	6.9707	5.48	19.090	41.86	18.405
30 minutes post-regadenoson dose	70	5.491	2.1355	2.35	4.985	11.55	5.113
60 minutes post-regadenoson dose	70	3.714	1.5874	1.65	3.290	10.91	3.449
120 minutes post-regadenoson dose	70	2.615	1.3219	1.05	2.290	8.17	2.358

The PKAS included all subjects who provided adequate pharmacokinetic samples, as defined by the pharmacokineticist, to calculate the primary pharmacokinetic parameters.

Max: maximum; Min: minimum; MPI: myocardial perfusion imaging; PKAS: pharmacokinetic analysis set.

Source: Table 12.4.1.7

Table 6 Day 5 Mean Regadenoson Pharmacokinetic Parameters

Treatment Group Parameter	n	Mean	SD	Min	Median	Max	Geometric mean
Placebo + Regadenoson MPI 3							
C_{max} (ng/mL)	66	20.943	8.7933	3.10	19.545	52.26	19.208
t_{max} (min)	66	4.6	6.38	2	3.0	38	3.6
AUC_{last} (min*ng/mL)	66	702.21708	389.622824	274.7834	628.69430	2605.7297	639.35542
CL_{tot} (mL/min)	66	500.56755	197.882660	144.2245	471.58780	1185.1356	463.99109
$t_{1/2}$ (min)	66	74.20318	23.824298	18.3569	73.36080	136.4189	69.96479
V_{ss} (mL)	66	52483.81673	21614.542708	4170.6826	51251.77050	106537.3913	46834.26615
Caffeine 200 mg + Regadenoson MPI 3							
C_{max} (ng/mL)	71	20.764	7.0953	5.81	20.360	38.07	19.489
t_{max} (min)	71	3.7	3.18	1	3.0	28	3.3
AUC_{last} (min*ng/mL)	71	677.93185	241.237803	318.2496	643.76980	1830.9199	643.54559
CL_{tot} (mL/min)	71	472.51149	166.414971	33.7925	450.56610	1035.8037	437.09365
$t_{1/2}$ (min)	71	84.05351	53.089384	32.5328	75.31030	494.9791	77.87567
V_{ss} (mL)	71	52263.12575	16729.807020	9267.8813	52289.20250	93807.8400	49107.83835
Caffeine 400 mg + Regadenoson MPI 3							
C_{max} (ng/mL)	70	19.420	7.2082	2.41	19.000	41.86	17.898
t_{max} (min)	70	4.2	4.55	3	3.0	30	3.5
AUC_{last} (min*ng/mL)	70	692.99622	237.035967	273.4263	627.67500	1544.9625	656.80369
CL_{tot} (mL/min)	70	436.26031	159.612101	153.7844	435.25670	844.9245	405.94234
$t_{1/2}$ (min)	70	96.15112	84.557318	46.7552	81.26390	743.4939	85.61943
V_{ss} (mL)	70	53718.31918	21501.133829	14553.6107	50334.13635	164954.5187	50143.10389

The PKAS included all subjects who provided adequate pharmacokinetic samples, as defined by the pharmacokineticist, to calculate the primary pharmacokinetic parameters.

Max: maximum; Min: minimum; MPI: myocardial perfusion imaging; PKAS: pharmacokinetic analysis set.

Source: Table 12.4.2.4

Table 7 Incidence of TEAEs in > 5% of Subjects

Preferred Term † (MedDRA V11.1)	Placebo + Regadenoson (n = 113) n (%)	Caffeine 200 mg + Regadenoson (n = 116) n (%)	Caffeine 400 mg + Regadenoson (n = 116) n (%)
Any AE	82 (72.6%)	89 (76.7%)	80 (69.0%)
Dyspnoea	43 (38.1%)	47 (40.5%)	34 (29.3%)
Headache	36 (31.9%)	37 (31.9%)	38 (32.8%)
Flushing	27 (23.9%)	29 (25.0%)	27 (23.3%)
Chest discomfort	22 (19.5%)	25 (21.6%)	19 (16.4%)
Dizziness	22 (19.5%)	25 (21.6%)	18 (15.5%)
Nausea	13 (11.5%)	16 (13.8%)	10 (8.6%)
Chest pain	8 (7.1%)	1 (0.9%)	2 (1.7%)
Stomach discomfort	7 (6.2%)	4 (3.4%)	4 (3.4%)
Abdominal discomfort	6 (5.3%)	3 (2.6%)	5 (4.3%)
Abdominal pain upper	6 (5.3%)	4 (3.4%)	5 (4.3%)
Dysgeusia	4 (3.5%)	11 (9.5%)	5 (4.3%)
Feeling hot	3 (2.7%)	5 (4.3%)	6 (5.2%)

The SAF included all randomized subjects who received at least 1 dose of regadenoson.

AE: adverse event; SAF: safety analysis set; TEAE: treatment emergent adverse event.

† Preferred terms are presented in order of decreasing frequency by placebo group.

Source: Table 12.6.1.6