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Name of Finished Product: Regadenoson		
Name of Active Ingredient: Regadenoson		

SYNOPSIS

Title of Study: A Phase 2, Open-Label, Randomized, Cross-Over Study of Regadenoson in Subjects Undergoing Stress Myocardial Perfusion Imaging by Multidetector Computed Tomography (MDCT) and Single Photon Emission Computed Tomography (SPECT)

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

Study Center(s): This phase 2 study was conducted at 11 sites in the United States (US).

Publication Based on the Study: None

Study Period: April 2011 to July 2012

Study Initiation Date (Date of First Enrollment): 26 April 2011

Study Completion Date (Date of Last Evaluation): 02 July 2012

Phase of Development: Phase 2

Objectives: The primary objective of this study was to establish the noninferiority of myocardial perfusion imaging (MPI) using MDCT with regadenoson as compared to SPECT with regadenoson in detecting the presence or absence of ischemia (number of reversible defects).

The secondary objectives were to assess the image quality of regadenoson computed tomography perfusion (CTP) and SPECT MPI scans; to compare the agreement between and the presence of reversible defects associated with each coronary vessel (left anterior descending coronary artery [LAD], right coronary artery [RCA], left circumflex coronary artery [LCX]) identified by CTP as compared to SPECT MPI; to evaluate the sensitivity and specificity of diagnostic accuracy with CTP as compared to SPECT for fixed defects; and to determine the percent of subjects who had 2 or more ischemic segments on SPECT, but less on computed tomography (CT) (false negative CT).

Methodology: This was a multicenter, open-label, randomized, cross-over study in subjects with typical angina who met at least 1 of the 3 following criteria: suspected (clinical impression) or known diagnosis of coronary artery disease (CAD) with typical angina that had been referred from nuclear cardiology lab schedule or cardiac CT schedule; stable symptoms with possible elective catheterization procedure scheduled and where further imaging might be beneficial; or known CAD from a previous invasive coronary angiography (ICA) performed more than 12 weeks prior to screening who presented with new cardiac symptoms.

Subjects were randomized to 1 of 2 imaging procedure sequences and to undergo both a rest and stress SPECT series and a rest and stress MDCT series. In the SPECT-MDCT sequence 1, subjects underwent a rest SPECT and a regadenoson stress SPECT procedure on day 1 and a regadenoson stress CTP and a rest CCTA/CTP

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procedure on day 2. In the MDCT-SPECT sequence, underwent a regadenoson stress CTP and a rest CCTA/CTP procedure on day 1 and a rest SPECT and a regadenoson stress SPECT procedure on day 2.

Subjects were administered open-label regadenoson 0.4 mg in a 5 mL intravenous bolus as a pharmacological stress agent prior to each stress CTP and stress SPECT procedure. At least 24 hours was stipulated between each dose of regadenoson. Although not required to be hospitalized, subjects were to remain at the study site for 2 hours on both day 1 and day 2 following the regadenoson dose for electrocardiogram (ECG), vital signs, physical examination and adverse event assessment.

A safety follow-up via telephone contact was scheduled on day 3; and a day 30 telephone follow-up call was scheduled for serious adverse event assessment and inquiry as to whether the subject required an ICA during the post study period.

Number of Patients (Planned, Enrolled and Analyzed): The planned number of subjects was 110. There were 124 subjects enrolled and randomized into the study: 63 subjects in sequence SPECT-MDCT and 61 subjects in sequence MDCT-SPECT.

Three analysis sets were used in the study. The Full Analysis Set (FAS) was composed of all randomized subjects with interpretable SPECT and CTP scans as determined by at least two of the three blinded readers. The Safety Analysis Set (SAF) was composed of all randomized subjects who received at least 1 dose of regadenoson. The Angiographic Analysis Set (AAS) was composed of all randomized subjects with interpretable SPECT, CCTA and CTP scans and interpretable ICA. The number of subjects in each treatment group for these analysis sets is presented in [Figure 1].

Diagnosis and Main Criteria for Inclusion: Subjects that were eligible to participate in this study were males ≥ 45 years of age and females ≥ 50 years of age with typical angina. Subjects had to meet at least 1 of the following 3 criteria: had a suspected (clinical impression) or known diagnosis of CAD with typical angina that had been referred from nuclear cardiology lab schedule or cardiac CT schedule; had stable symptoms with possible elective catheterization procedure scheduled and where further imaging might be beneficial; or had known CAD from a previous ICA performed more than 12 weeks prior to screening who currently presented with new cardiac symptoms. Subjects had to have been referred for a clinically indicated myocardial perfusion imaging procedure or cardiac CT procedure for suspected moderate or high risk CAD. Subjects were to abstain from eating and drinking (30 minutes prior to and 30 minutes post study drug administration), consuming methylxanthine-containing foods and beverages (12 hours prior to day 1 visit through the day 3 follow-up visit), smoking (3 hours prior to and 8 hours post study drug administration) and theophylline (12 hours prior to study drug administration). All subjects were required to sign the written subject informed consent form.

Test Product, Dose and Mode of Administration: Lexiscan® (regadenoson) was administered as a single intravenous bolus injection of 0.4 mg in 5 mL over approximately 10 seconds. Regadenoson stress CTP was performed in sequence prior to rest CCTA/CTP imaging, regardless of randomization sequence. Resting

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SPECT imaging was performed in sequence prior to regadenoson stress SPECT imaging, regardless of randomization sequence. Manufacturer's lot number [redacted] was used in the study.

Duration of Treatment (or Duration of Study, if applicable): Subjects were administered a single dose of regadenoson prior to each stress CTP and stress SPECT procedure. Each subject had one rest and one regadenoson stress procedure on day 1 and day 2.

Criteria for Evaluation: The primary variable was the number of reversible defects categorized into absence or presence of ischemia (0 – 1 versus 2 or more), as assessed by the central imaging laboratory for both SPECT and MDCT. The secondary variables were overall image quality as assessed by independent blinded readers; the absence or presence of reversible defects (0 – 1 versus ≥ 2) in each of 3 regions of defect localization (LAD, RCA, LCX); the presence of 1 or more fixed perfusion defects as assessed by the central imaging laboratory; and the number of subjects who had 2 or more ischemic segments on SPECT, but less on CT (false negative CT).

Safety was assessed by evaluation of treatment-emergent adverse events (severity, seriousness and relationship to regadenoson), clinical laboratory variables (hematology, biochemistry), vital signs (systolic and diastolic blood pressure, heart rate and respiratory rate), physical examination and 12-lead electrocardiogram (ECG).

Statistical Methods: The following populations were defined for the analyses:

- Full Analysis Set (FAS): all randomized subjects with interpretable SPECT and CTP scans as determined by at least two of the three blinded readers. All efficacy analyses were performed using this set unless otherwise specified.
- Safety Analysis Set (SAF): all randomized subjects who receive at least 1 dose of regadenoson.
- Angiographic Analysis Set (AAS): all randomized subjects with interpretable SPECT, CCTA and CTP scans and interpretable ICA.

For continuous variables, descriptive statistics included the number of subjects (n), mean, standard deviation, median, minimum and maximum. The mean values were compared between treatment modalities using a one-way analysis of variance (ANOVA).

Discrete variables were summarized by number/percent of subjects in each category. Treatment modalities were compared using McNemar's test at the $\alpha = 0.05$ significance level unless specifically stated otherwise. All null hypotheses were of no treatment difference. All alternative hypotheses were 2-sided.

For the purpose of analysis, a treatment-emergent adverse event was defined as an adverse event observed from the time of administration of regadenoson to 24 hours after study drug administration within each modality. If a subject experienced an event both during the pre-investigational period and during the investigational period of the first study drug dose or if a subject experienced an event both during the investigational period of the first study drug dose and during the investigational period of the second study drug dose, the event was considered to

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be a treatment-emergent adverse event only if it had worsened in severity (i.e., it was reported with a new start date).

Summary of Results/Conclusions:

Population: The mean age of subjects included in the SAF was 61.6 years (range 45 to 85 years). The population was primarily white (89.8%) and male (72.0%). No significant differences were identified between the randomized treatment sequences in terms of any demographic variable or baseline weight and BMI [Table 1].

The mean age of subjects included in the FAS was 61.7 years (range 45 to 85 years). This population was primarily white (90.0%) and male (70.9%). No significant differences were identified between the randomized treatment sequences in terms of any demographic variable or baseline weight and BMI [Table 12.1.2.2.1].

Most subjects in both the SAF (96.6%) and FAS (98.2%) were enrolled and randomized following Amendment 1 of the protocol [Table 1; Table 12.1.2.2.1]. Changes in protocol procedures were applied uniformly to all subjects and did not prejudice study outcome or data analysis.

Primary Efficacy Results: In the primary assessment of the presence of cardiac ischemia, regadenoson stress SPECT imaging identified 100 subjects as having 0 – 1 reversible defects and 10 subjects as having ≥ 2 reversible defects. In comparison, regadenoson stress CTP imaging identified 85 and 25 subjects as having 0 – 1 or ≥ 2 reversible defects, respectively. The agreement rate between regadenoson stress SPECT and regadenoson stress CTP was 87% (95% CI: 77%, 97%) [Table 2]. The lower boundary of this 95% CI was within 0.15 of 0.78 (defined as the threshold for noninferiority); therefore, regadenoson stress CTP was determined to be noninferior to regadenoson stress SPECT in the primary analysis.

Using SPECT as the reference standard for the presence of ischemia (number of reversible defects), the specificity for regadenoson stress CTP to detect ischemia was 84% and sensitivity was 90% [Table 12.3.1.1.1].

Safety Results: The most common treatment-emergent adverse events were flushing, with an overall incidence of 33.9% (15.4% and 22.4% of subjects in the SPECT and MDCT modalities, respectively) and headache, with an overall incidence of 25.4% (12.8% and 19.8% of subjects in the SPECT and MDCT modalities, respectively) [Table 3]. All remaining treatment-emergent adverse events were reported by ≤ 11.1% of subjects in either modality group. All cases of flushing (n = 40) and 24 of 30 cases of headache were considered drug-related [Table 12.6.1.2 and Table 12.6.1.3] and all cases of both events were categorized as mild or moderate in intensity [Table 12.6.1.4]. Of the total 265 treatment-emergent adverse events reported during the study, 7 events (2 for SPECT and 5 for MDCT) were categorized as severe [Table 4].

One treatment-emergent serious adverse event was reported during the study. Subject [redacted] ([redacted]): Severe gastritis onset day 2 following SPECT imaging met the serious adverse event criterion "other medically important event" [Section 5.4.3.1]. The investigator determined the serious adverse event was not related to study drug but study drug was withdrawn due to the event [Section 9.1.3.3].

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Serious adverse events were captured for a time range beginning with the first dose of study drug on day 1 through 30 days post study drug. Detailed narratives for all recorded serious adverse events are provided in [Attachment 1].

CONCLUSIONS: The primary analysis of Study 3606-CL-2001 confirmed that regadenoson stress CTP was noninferior to regadenoson stress SPECT in detecting the presence or absence of ischemia (number of reversible defects).

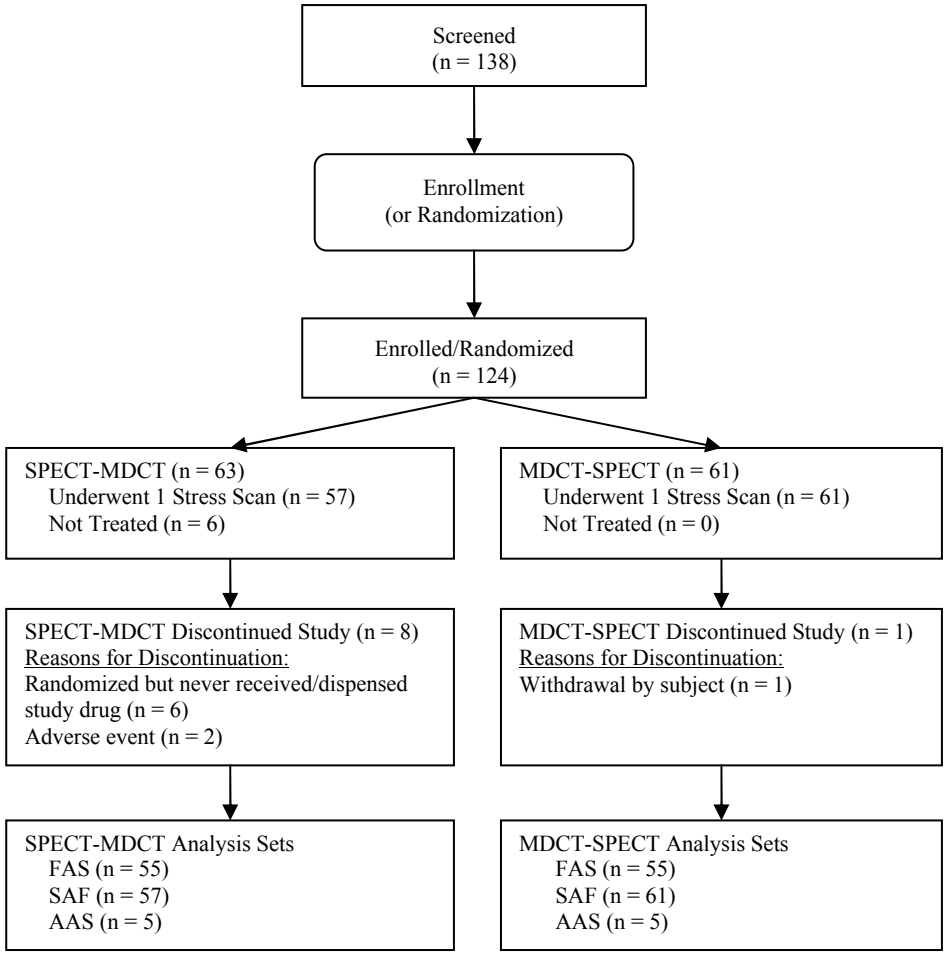
Results of secondary objectives supported these conclusions:

- Image quality as assessed by independent blinded reviewers was generally described as excellent to good for rest and stress SPECT, and good to fair for rest and stress CTP.
- Subanalyses of ischemia within various coronary artery regions was consistent with the results of the primary analysis, and the rates of ischemia were consistent across the three coronary arteries analyzed (LAD, RCA, LCX). Agreement rates between the two imaging modalities for detecting ischemia when defined as ≥ 2 reversible defects were high for LAD and LCX (95% and 79% respectively), but lower for RCA (47%). This difference in agreement rates was no longer present when considering ischemia defined ≥ 1 reversible defect, as agreement rates ranged between 74% and 95%.
- Regadenoson stress CTP identified n = 25 subjects with cardiac ischemia, while SPECT identified n = 10. Using SPECT as a reference standard for the presence of ischemia by a variety of criteria (≥ 2 reversible defects, ≥ 1 reversible defect, or ≥ 1 fixed defect), the specificity and sensitivity for regadenoson stress CTP to detect ischemia were consistently high (range: 77 – 95%). Overall, the false negative percent for CTP relative to SPECT imaging was low (10%), as 9 of the 10 subjects identified by SPECT to have cardiac ischemia were identified by regadenoson stress CTP to have ischemia as well.
- Administration of regadenoson was well tolerated in this study. Adverse events observed in this population were consistent with the known safety and tolerability profile of regadenoson, and safety profiles were not different across imaging modalities. The mean total radiation dose (rest plus stress imaging) was higher for the MDCT imaging procedure (17.7 ± 6.8 mSv) compared with the SPECT imaging procedure (11.2 ± 1.8 mSv).

In conclusion, in this population of subjects with known or suspected CAD, regadenoson stress MDCT imaging demonstrated satisfactory sensitivity and specificity to detect cardiac ischemia, with a similar tolerability profile, as compared to SPECT imaging.

Date of Report: 02 May 2013

Figure 1 Disposition of Subjects



FAS: Full Analysis Set composed of all randomized subjects with interpretable SPECT and CTP scans as determined by at least two of the three blinded readers.

SAF: Safety Analysis Set composed of all randomized subjects who received at least 1 dose of regadenoson.

AAS: Angiographic Analysis Set composed of all randomized subjects with interpretable SPECT, CCTA and CTP scans and interpretable ICA.

MDCT: multidetector computed tomography; SPECT: single photon emission computed tomography

Source: Tables 12.1.1.1, 12.1.1.2 and 12.1.1.3

Table 1 Demographic Characteristics

Parameter Category/Statistic	Regadenoson SPECT-MDCT (n = 57)	Regadenoson MDCT-SPECT (n = 61)	Total (n = 118)	P Value
Sex, n (%)				
Male	39 (68.4)	46 (75.4)	85 (72.0)	0.40†
Female	18 (31.6)	15 (24.6)	33 (28.0)	
Race, n (%)				
White	52 (91.2)	54 (88.5)	106 (89.8)	0.50†
Black or African American	2 (3.5)	5 (8.2)	7 (5.9)	
Asian	3 (5.3)	2 (3.3)	5 (4.2)	
Ethnicity, n (%)				
Non-Hispanic or –Latino	37 (64.9)	41 (67.2)	78 (66.1)	0.79†
Hispanic or Latino	20 (35.1)	20 (32.8)	40 (33.9)	
Age (years)				
Mean (SD)	60.8 (9.19)	62.3 (9.41)	61.6 (9.29)	0.67‡
Median	61.0	62.0	61.5	
Minimum - Maximum	47 - 79	45 - 85	45 - 85	
Weight (kg)				
Mean (SD)	85.54 (16.836)	88.85 (20.116)	87.25 (18.600)	0.63‡
Median	83.60	90.20	85.30	
Minimum - Maximum	49.4 - 144.1	50.5 - 159.1	49.4 - 159.1	
BMI (kg/m^2)				
Mean (SD)	29.03 (5.57)	30.02 (5.10)	29.54 (5.33)	0.60‡
Median	28.96	29.89	29.35	
Minimum - Maximum	18.3 - 45.1	21.0 - 45.0	18.3 - 45.1	
Enrolled Under, n (%)				
Original protocol	2 (3.6)	2 (3.3)	4 (3.4)	NC
Protocol amendment 1	55 (96.5)	59 (96.7)	114 (96.6)	

Safety Analysis Set (SAF): All randomized subjects who received at least 1 dose of regadenoson.

SPECT: Single Photon Emission Computed Tomography; MDCT: Multidetector Computed Tomography; BMI: body mass index; NC: not calculated

† Chi-squared test.

‡ One-way ANOVA.

Source: Table 12.1.2.1.2

Table 2 Primary Efficacy Criteria: Agreement Between SPECT and CTP with Respect to Presence of Ischemia Defined by the Number of Reversible Defects

	Number of Reversible Defects	Regadenoson CTP			Agreement Rate ± SE (95% CI†)
		0 - 1	≥ 2	All	
Regadenoson SPECT	**0 - 1**	84	16	100	0.87 ± 0.051 (0.77, 0.97)
	≥ 2	1	9	10	
	All	85	25	110	

Full Analysis Set (FAS): All randomized subjects with interpretable SPECT and CTP scans as determined by at least two of the three blinded readers.

Regadenoson SPECT: stress Single Photon Emission Computed Tomography; Regadenoson CTP: stress Computed Tomography Perfusion; SE: standard error; CI: confidence interval.

Scoring based on 17-segment model for standardized myocardial segmentation: 0 = normal perfusion; 1 = mild reduction in counts, not definitely abnormal; 2 = moderate reduction in counts, definitely abnormal; 3 = severe reduction in counts; 4 = absent uptake.

† Predefined noninferiority criterion: If the lower boundary of the 95% CI was within 0.15 of 0.78, MDCT would be determined to be noninferior to SPECT.

Source: Table 12.3.1.1.1

Table 3 Treatment-emergent Adverse Events Reported in at Least 5% of Subjects in Either Treatment Sequence Classified by System Organ Class and Preferred Term

MedDRA (V11.1) System Organ Class Preferred Term	Number of Patients (%) Regadenoson SPECT (n = 117)	MDCT (n = 116)	Total (n = 118)
Overall	**53 (45.3)**	**59 (50.9)**	**81 (68.6)**
Nervous System Disorders	**25 (21.4)**	**31 (26.7)**	**45 (38.1)**
Headache	15 (12.8)	23 (19.8)	30 (25.4)
Dizziness	11 (9.4)	6 (5.2)	16 (13.6)
Vascular Disorders	**19 (16.2)**	**26 (22.4)**	**41 (34.7)**
Flushing	18 (15.4)	26 (22.4)	40 (33.9)
Gastrointestinal Disorders	**18 (15.4)**	**14 (12.1)**	**25 (21.2)**
Nausea	9 (7.7)	6 (5.2)	11 (9.3)
General Disorders and Administration Site Conditions	**11 (9.4)**	**11 (9.5)**	**19 (16.1)**
Chest discomfort	11 (9.4)	9 (7.8)	17 (14.4)
Respiratory, Thoracic and Mediastinal Disorders	**14 (12.0)**	**11 (9.5)**	**17 (14.4)**
Dyspnoea	13 (11.1)	10 (8.6)	16 (13.6)
Cardiac Disorders	**5 (4.3)**	**12 (10.3)**	**15 (12.7)**
Angina pectoris	4 (3.4)	9 (7.8)	11 (9.3)

Safety Analysis Set (SAF): All randomized subjects who receive at least 1 dose of regadenoson.

Regadenoson SPECT: stress Single Photon Emission Computed Tomography; Regadenoson MDCT: stress Multidetector Computed Tomography

Treatment-emergent adverse event: An adverse event observed from the time of administration of regadenoson to 24 hours after study drug administration within each modality.

Source: Table 12.6.1.2

Table 4 Severe Treatment-emergent Adverse Events

Subject (Modality)	Age†/Sex/ Race	MedDRA Preferred Term (Investigator's Verbatim Term)	Last Dose Day	Onset/ Stop Day	Outcome/ Duration‡	Relationship to Study Drug
[redacted] (SPECT) (MDCT)	[redacted]	Angina pectoris ([redacted])	2	1/1	Recovered/ 20 minutes	Probable
		Angina pectoris ([redacted])	2	2/2	Recovered/ 46 minutes	Probable
[redacted] (SPECT)	[redacted]	Gastritis ([redacted])§ ¶	1	2/2	Recovered/ 8 hours	Not related
[redacted] (MDCT)	[redacted]	Pain in jaw ([redacted])	3	3/3	Recovered/ 14 minutes	Probable
		Angina pectoris ([redacted])	3	3/3	Recovered/ 13 minutes	Probable
[redacted] (MDCT)	[redacted]	Dyspnoea ([redacted])	3	1/1	Recovered/ 7 minutes	Probable
[redacted] (MDCT)	[redacted]	Vomiting ([redacted])	6	1/1	Recovered/ 1 episode	Possible

Treatment-emergent adverse event: An adverse event observed from the time of administration of regadenoson to 24 hours after study drug administration within each modality.

MDCT: Multidetector Computed Tomography; SPECT: Single Photon Emission Computed Tomography

† Age in years.

‡ Approximate duration.

§ Reported as other medically important event.

¶ Drug withdrawn.

Source: Table 12.6.1.4, Appendix 13.2.7.2 and Appendix 13.2.7.4