ABBREVIATED CLINICAL STUDY REPORT

Study Title:	An Open-Label, Parallel-Group, Exploratory Study to Evaluate the Efficacy and Safety of 400 µg Regadenoson Bolus for Pharmacological Stress Echocardiography
Name of Test Drug:	Regadenoson
Dose and Formulation:	Regadenoson Solution for Injection, 0.08 mg/mL
Indication:	Stress echocardiography
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	CVT 5127
Phase of Development:	Phase 2
IND No.:	Not applicable
EudraCT No.:	2008-003839-20
Study Start Date:	07 May 2009 (First Patient Screened)
Study End Date	29 April 2010 (Last Patient Observation)
Principal or Coordinating Investigator:	Name: Professor Roxy Senior, MD Affiliation: [redacted] PPD
Gilead Responsible Medical Monitor:	Name: David Kwon, MD Telephone: PPD Fax: PPD
Report Date:	14 January 2011

CONFIDENTIAL AND PROPRIETARY INFORMATION

This study was conducted in accordance with the guidelines of Good Clinical Practice, including archiving of essential documents.

STUDY SYNOPSIS
Study CVT 5127
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404 USA

Title of Study: Study CVT 5127: An Open-Label, Parallel-Group, Exploratory Study to Evaluate the Efficacy and Safety of 400 μg Regadenoson Bolus for Pharmacological Stress Echocardiography
Investigators: Professor Roxy Senior, MD
Study Centers: Northwick Park Hospital, Harrow, Middlesex, United Kingdom
Publications: None
Study Period: 07 May 2009 (First patient screened) 29 April 2010 (Last patient observation)
Phase of Development: Phase 2
Objectives: The primary objective of this study was to evaluate the efficacy of a 400 μg regadenoson bolus for pharmacological stress echocardiography by comparing the stress echocardiographic images obtained after dobutamine with those obtained after regadenoson alone, regadenoson with low-level exercise (25 Watts [W]), regadenoson with echocontrast agent, and by comparing perfusion stress echocardiography (PSE) images obtained after dipyridamole with those obtained after regadenoson. The secondary objective was to evaluate the safety of regadenoson as a pharmacologic stress agent for echocardiography.

Methodology: This was an open-label, nonrandomized, parallel-group exploratory study that investigated the efficacy and safety of a regadenoson bolus for pharmacological stress echocardiography in comparison to dobutamine stress echocardiography**,** and in comparison to dipyridamole PSE. Patients received open-label regadenoson in one of 5 groups, as follows:

- Group A: Regadenoson wall motion stress echocardiogram compared to dobutamine stress echocardiogram.
- Group B: Regadenoson wall motion stress echocardiogram (without contrast agent) during low-level exercise (25 W for 5 minutes on an ergometer [in a semi-supine or supine position]) compared to dobutamine stress echocardiogram.
- Group B-1: Regadenoson wall motion stress echocardiogram with the echocontrast agent SonoVue® during low-level exercise (25 W for 5 minutes on an ergometer [in a semi-supine or supine position]) compared to dobutamine stress echocardiogram with SonoVue.
- Group C: Regadenoson wall motion stress echocardiogram with SonoVue compared to dobutamine wall motion stress echocardiogram with SonoVue
- Group D: Regadenoson PSE with SonoVue compared to dipyridamole PSE with SonoVue

The interval between the end of the infusion for the qualifying echocardiogram and the start of the baseline evaluations for the regadenoson stress echocardiogram was to be between approximately 24 hours and 8 weeks.

If a clinically indicated coronary angiogram was performed within approximately 8 weeks before or after the regadenoson stress echocardiogram, the results of the angiogram were collected if available.

During the study, patients were monitored continuously after receiving study drug and observed for 2 hours after dosing. A follow-up assessment (telephone call) was conducted 24-72 hours after regadenoson dosing.

Aminophylline (a nonspecific adenosine receptor blocker) was to be available at the bedside of the patient during regadenoson dosing and throughout the entire observation period. Aminophylline was to be administered to attenuate severe and/or persistent adverse reactions (eg, angina, headache, electrocardiogram [ECG] ST segment depression, and chest pain). For patients in Group D, aminophylline was also to be available during dipyridamole dosing, as appropriate.

Images obtained after the qualifying echocardiogram and after regadenoson stress echocardiography for each patient were forwarded to a core laboratory for reader assessments of wall motion or perfusion abnormalities, wall motion scores, and image quality. (Note, the reader was blinded to treatment group, and the images were read in random order.) Available angiograms were also evaluated at the core laboratory for the presence of stenosis.

Due to slow patient enrollment, the study was stopped early by the sponsor.

Number of Subjects (Planned and Analyzed):

Planned: 40 patients were planned: up to 10 patients in Groups A and B combined were to be treated, and up to 10 patients in each of Groups B-1, C and D were to be treated.

Analyzed: A total of 22 patients were dosed with regadenoson (3 in Group A, 1 in Group B, 1 in Group B-1, 10 in Group C, and 7 in Group D); all dosed patients were included in the efficacy and safety analyses.

Diagnosis and Main Criteria for Inclusion: Eligible patients were males or females ≥ 18 years of age, having adequate intravenous access in both arms, willing to comply with the requirements of the protocol, and providing written informed consent. Female patients were to be not pregnant, not lactating, and either postmenopausal, surgically sterilized, or using an adequate contraceptive method.

Patients in Groups A, B, B-1, and C were to have undergone a clinically indicated dobutamine stress echocardiogram with normal images at rest and definitive reversible wall motion abnormalities during stress. In addition, patients in Groups B and B-1 were to be capable of low-level exercise (ergometer exercise test with a constant workload of 25 W for 5 minutes). For patients in Groups B-1 and C, the dobutamine stress echocardiogram was to be performed with SonoVue.

Patients in Group D were to have undergone a clinically indicated dipyridamole PSE with SonoVue (either prior to or at screening), resulting in a qualifying dipyridamole PSE (digitally recorded) that shows normal perfusion and generally normal wall motion (defined as ≤ 2 segments with wall motion abnormalities) at rest and definitively abnormal perfusion with or without abnormal wall motion during stress.

During the interval between the clinically indicated dobutamine (Groups A, B**,** B-1 and C) or dipyridamole (Group D) stress echocardiogram and the regadenoson stress echocardiogram, patients must have had a stable medical condition (no change in symptoms), no change in cardioactive medications, and no coronary intervention (percutaneous transluminal coronary angioplasty or stenting).

Among other criteria, patients were not eligible for participation in the study if they experienced a serious reaction during the clinically-indicated dobutamine stress echocardiogram or dipyridamole PSE.

Duration of Treatment: Patients received a single iv bolus of regadenoson.

Test Product, Dose, Mode of Administration, and Batch No.: In all groups, regadenoson was administered as an iv bolus of 400 µg over approximately 10 seconds, followed immediately by a 5-mL saline flush.

Batch numbers of regadenoson used in the study were 902624 and 911106.

Criteria for Evaluation:

Efficacy: The primary efficacy endpoint for Groups A, B, B-1, and C was the reader's qualitative global assessment of wall motion over the entire left ventricle (LV). Secondary efficacy variables for these groups included the following: the qualitative assessment of wall motion in the left anterior descending (LAD) coronary artery and in non-LAD (left circumflex [LCx] and right coronary artery [RCA]) territories; wall motion index, scored on a 5-point scale (1=normal, 2=mildly hypokinetic, 3=severely hypokinetic, 4=akinetic anywhere in the region, 5=dyskinetic); and image quality (1=excellent, 2=good, 3=fair, 4=poor).

The primary efficacy variable for Group D was the reader's qualitative global assessment of perfusion over the entire LV. Secondary efficacy variables for this group included the following: the qualitative assessment of perfusion in LAD and in non-LAD territories; qualitative assessment of perfusion by segment; qualitative assessment of wall motion in the entire LV and in LAD and non-LAD territories; quantitative estimates of rest and stress peak intensity and refilling rate (A, β) for the LAD, RCA, and LCx coronary artery territories; image quality (1=excellent, 2=good, 3=fair, 4=poor).

If available, angiography results were compared with wall motion and perfusion assessments.

Catecholamine (norepinephrine and epinephrine) levels, immediately prior to regadenoson dosing and up to 60 minutes following dosing, were assessed for patients in Groups A and B.

Safety: The safety of regadenoson was assessed through treatment-emergent adverse events (AEs), identification of serious adverse events (SAEs), clinical laboratory tests, vital signs, ECGs, and use of aminophylline to reverse adverse effects of regadenoson.

Statistical Methods:

Data were summarized by treatment group (Groups A, B, and B-1 pooled [n=5], Group C [n=10], and Group D [n=7]), and all patients pooled (n=22). Categorical variables were summarized with counts and percentages. Continuous variables were summarized with mean, standard deviation (SD) or standard error, median, minimum, and maximum, and if appropriate, count. Due to the small sample size, no statistical analyses were performed beyond simple summary statistics.

Efficacy: The percent of patients with abnormal peak stress wall motion under regadenoson and under either dobutamine or dipyridamole for the entire LV and by region were summarized; and for Group D only, the percent of patients with abnormal peak stress perfusion under regadenoson and under dipyridamole for the entire LV and by region were summarized. Primary and secondary read wall motion assessments and qualitative and quantitative perfusion results (Group D only) were listed.

Angiography results were listed by patient, side-by-side with wall motion and perfusion assessments for comparison. Image quality results were listed by patient.

Safety: Adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) thesaurus, version 13. Summaries of AEs were restricted to events with onset date/time (or possible onset date-time, in the case of incomplete date/times) later than or equal to the date/time of regadenoson dosing and onset date (or possible date) no later than 3 days after the date of regadenoson dosing. Events were tabulated by system organ class and preferred term. AE summaries included the number and proportion of patients in each treatment group who experienced: (1) at least one AE, (2) at least one AE considered by the investigator as possibly or probably related to study treatment, (3) at least one severe AE, and (4) at least one SAE.

All safety laboratory data collected were listed in original and standard units for predose values, postdose values, and changes from baseline (predose). Values outside of normal ranges, using standard units, were flagged. Quantitative assessments were summarized using descriptive statistics by treatment group and for all groups combined.

Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and rate-pressure product at each time point were listed and summarized by treatment group, with descriptive statistics for measured values and changes from baseline. ECG intervals (ventricular rate, PR, QRS, QT, and QTc [using the Fridericia correction formula] were listed.

SUMMARY – RESULTS:

Subject Disposition and Demographics: A total of 22 patients (3 in Group A, 1 each in Groups B and B-1, 10 in Group C, and 7 in Group D) enrolled in the study and received a single iv bolus dose of 400 µg regadenoson. The patients consisted of 13 men (59%) and 9 women (41%); the mean age was 64 years (range, 43 to 80 years), and the majority were Asian (14 [64%]). Cardiovascular history included stable angina (68% of patients), coronary artery disease (64% of patients), and hypertension (50% of patients).

Efficacy Results: Peak stress wall motion assessments were compared between regadenoson scans and dobutamine scans. Although the number of patients examined was small, regadenoson given as an iv bolus of 400 μg did not seem to consistently evoke wall motion abnormalities compared to dobutamine.

In addition, peak stress perfusion assessments of images obtained following regadenoson administration were compared to those obtained following dipyridamole administration. When available, results were compared to angiography data. Because there was inconsistent agreement and with only a few patients in each of the groups evaluated, the data collected for perfusion analysis are considered inconclusive.

Safety Results: Adverse events were reported for 11 of the 22 patients in this study. The most frequently reported AEs (ie, by more than 2 patients) were respiratory rate increased (6 patients), abdominal discomfort (3 patients), and dizziness (3 patients). Most of the AEs were characterized as mild in intensity; 2 patients had an AE of greater intensity: one patient had severe dizziness and another patient had severe hemoglobin decreased. This latter AE required hospitalization and was therefore categorized as an SAE (the only SAE reported during this study). All AEs, except hemoglobin decreased, were considered by the investigator as related to study drug. Three patients had an AE that led to use of aminophylline; the AEs included headache, abdominal discomfort, upper abdominal pain, and dizziness. There were no deaths, and no patient discontinued from the study due to a treatment-emergent AE. No clinically significant trends in laboratory parameters were noted. Changes in vital signs observed following dosing (increased HR, decreased blood pressure, and increased rate-pressure product) were expected based on the pharmacodynamic properties of regadenoson. No clinically significant changes in ECGs and physical examination findings were observed.

CONCLUSIONS:

- Although few patients were evaluated, in comparison to dobutamine stress echocardiography, regadenoson is not a useful stress agent for stress echocardiography.
- With inconsistent agreement and only a few patients in each of the groups evaluated, the data are inconclusive as to whether regadenoson is a comparable pharmacologic stress agent in perfusion stress echocardiography.
- Catecholamine levels (specifically norepinephrine) appeared to increase following administration of regadenoson; however, too few patients were evaluated to adequately characterize the catecholamine response.
- A single iv bolus dose of 400 μg regadenoson was well tolerated by patients in this study.