# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**22-161**

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

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|---|---|---|---|
| *NDA* | 22161 | *Submission Date(s)* | May 14, 2007 |
| *Brand Name* | | Regadenoson (Lexiscan®) | |
| *Generic Name* | | N/A | |
| *Reviewer* | | Christy S. John, Ph.D | |
| *Team Leader* | | Young Moon Choi, Ph.D. | |
| *OCP Division* | | V | |
| *ORM Division* | | Division of Medical Imaging and Hematology Drug Products | |
| *Sponsor* | | CV Therapeutics, Inc | |
| *Relevant IND(s)* | | 62,862 | |
| *Submission Type; Code* | | S | 1 |
| *Formulation; Strength(s)* | | Intravenous bolus (<10 sec), (0.08 mg/mL), volume of injection (5 mL followed by 5 mL saline flush) | |
| *Indication* | | [redacted] | |

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# 1 Executive Summary

LEXISCAN™ (Regadenoson Injection) is a pharmacologic stress agent to be used in conjunction with radionuclide myocardial perfusion imaging (MPI). Regadenoson is chemically described as adenosine, 2-[4-[(methylamino)carbonyl]-1H-pyrazol-1-yl]-, monohydrate. Eight clinical pharmacology studies were performed by the sponsor in support of this NDA. These included a double-blind, randomized, placebo-controlled crossover, dose-escalation (0.1- 30 μg/kg), tolerability, safety and PK study in healthy volunteers. Peak plasma regadenoson concentrations were attained rapidly following dosing, with Tmax(obs) observed between 0.017 and 0.067 h post-dose throughout. Following Tmax(obs), there was evidence of a multi-exponential decline and is best characterized by 3-compartment model. Terminal elimination half life ($t_{½el}$) was ranged from 1.41 to 4.09 hours across all subjects. Increases in Cmax were proportional across the entire dose range from 0.1 to 20.0 μg/kg. Renal excretion of unchanged drug amounted to on average 57% with no relationship to the dose administered.

The dose was formulated as 0.08 mg/mL concentration of regadenoson in the 15% polyethylene glycol formulation, in order to deliver the dose in a 5 mL volume. Escalating doses of regadenoson were evaluated in healthy volunteers until a maximum tolerated dose (MTD) was achieved. A clinical dose of 0.4 mg in 5 mL was used in clinical studies and is proposed for marketing.

In the renal impairment study, regadenoson does cause a transient increase in QTc. The adverse events reflected the pharmacological effect of the drug and were related to vasodilation and an increase in HR. The most frequently reported drug-related adverse events included palpitation, vasodilation, dizziness, and ECG T-wave inversion. ECG abnormalities were clinically significant (T-wave inversion and ST segment depression), occurred only after dosing with regadenoson. Generally, these abnormalities occurred at the 3.0 μg/kg dose level and were most frequent at the 20.0 μg/kg dose level. ECG abnormalities occurred within 1.2 min of dosing and resolved within a few (15-60) minutes.

Renal function had a pronounced effect on renal clearance of regadenoson and its total renal clearance values. Renal clearance decreased from 22.4 (L/h) in control group to 10.3, 7.3 and 2.3 L/h in mild, moderate and severe renal impairment groups, respectively. The exposure ($AUC_{0\text{-}inf}$) increased

from 11.7 ng-h/mL in control group to 28.2 ng-h/mL in severe renal impaired group. The administration of regadenoson was associated with a rapid increase in heart rate in all our treatment groups. The mean increase from baseline was greatest at 2 min post-dose, returning to within 10 bpm of baseline after 15-60 min. Tachycardia was frequently reported as an adverse event. At 2 min after the regadenoson bolus, all four treatment groups showed a mean increase in QTc that resolved by 15 to 30 minute time point. A dose adjustment is not necessary for the renally impaired patients as the increase in Cmax is not significant, most adverse (HR, increase in QTc) events are transient and return to baseline within few minutes and appear to be related to Cmax. The drug injection and imaging procedure is performed in a hospital setting in the presence of a physician. Therefore, the risk (if any) can be managed easily by health care providers.

## 1.1 Recommendations:

The Office of Clinical Pharmacology, Division of Clinical Pharmacology V has reviewed NDA 22-161. The application was found to be acceptable from a clinical pharmacology perspective.

## 1.2 Phase IV Commitments

None

## 1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings:

Pharmacologic stress agents in radionuclide Myocardial Perfusion Imaging (MPI) studies with radiopharmaceuticals such as thallium-201 (Tl-210), technetium-99m sestamibi or tetrofosmin are used in the detection and functional characterization of ischemic heart disease and blood flow to the myocardium. The radiopharmaceuticals listed above are shown to distribute proportionally to myocardial blood flow. In an MPI study, two images are obtained: one image is obtained at rest and a second under a condition that increases coronary blood flow (CBF) using either exercise or using a pharmacologic stress agent (coronary vasodilator) which stimulates the increase in CBF caused by exercise. In patients with significant coronary artery disease (CAD) a redistribution of CBF occurs with an increase in

blood flow to normal coronaries due to vasodilation, and a relative decrease of blood flow in stenotic arteries. This "coronary steal" translates into less perfused regional myocardium area which can be imaged (detected) with radionuclide tracers. Adenoscan (adenosine) and dipyridamole are two drugs approved by the Agency as pharmacologic stress agents.

LEXISCAN™ (Regadenoson Injection) is a pharmacologic stress agent to be used in conjunction with radionuclide myocardial perfusion imaging (MPI). Peak plasma regadenoson concentrations were attained rapidly following dosing, with Tmax(obs) observed between 0.017 and 0.067 h post-dose. Following Tmax(obs), there was evidence of a multi-exponential decline and is best characterized by 3-compartment model. Terminal elimination half life ($t_{½el}$) ranged from 1.41 to 4.09 hours across all subjects. Clearance exhibited a similar level of variability ranging from 263.5 to 890.4 ml/h. Systemic exposure (AUC(0-t) and AUC(0-inf)) increased in proportion to the dose. In addition, increases in Cmax were largely proportional across the entire dose range from 0.1 to 30.0 µg/kg.

The selection of dose for Phase III clinical trials was based upon results from a Phase II, open-label, single-dose study in subjects undergoing a clinically indicated cardiac catheterization. This was a dose-escalation study, evaluating up to five dose levels: 30, 100, 300, 400, and 500 µg regadenoson. Doses were identified that increased average peak velocity (APV) (a procedure that measures the blood flow increase to coronary) to twice the baseline level for at least 2 minutes and that was well tolerated. APV measurements were performed by pulsed-wave Doppler ultrasonography. The evaluated doses of regadenoson that resulted in at least a 2-fold increase in mean APV from baseline for at least 2 minutes were 300, 400, and 500 µg. At the 400 µg and 500 µg doses, the effect was more sustained in terms of magnitude and duration of response; peak flow was 2.5 times baseline for a median duration of 2.79 minutes and 2.85 minutes, respectively. A 400 µg dose was therefore, chosen for Phase III clinical trials.

In the renal impairment study, regadenoson causes a transient increase in QTc. The adverse events reflected the pharmacological effect of the drug and were related to vasodilation and an increase in HR. The most frequently reported drug-related adverse events included palpitation, vasodilation, dizziness, and ECG T-wave inversion. ECG abnormalities were clinically significant (T-wave inversion and ST segment depression), occurred only

after dosing with regadenoson. Generally, these abnormalities occurred at dose level 3.0 μg/kg and were most frequent at the 20.0 μg/kg dose level. ECG abnormalities occurred within 1.2 min of dosing and resolved within a few (15-60) minutes. These adverse events appeared to be transient and can be easily managed as the drug is administered only in hospital settings in the presence of a licensed physician or nurse.

Incubation with human liver microsomes as well as human hepatocytes did not produce any detectable metabolites of regadenoson. Following intravenous administration of C-14 radiolabeled regadenoson to rats and dogs, approximately 90% of dose was recovered in 24-48 hrs in urine and feces (37% and 54%, respectively, in both species). These findings indicate that metabolism of regadenoson does not play a major role in the elimination of the drug.

Renal function had a pronounced effect on renal clearance of regadenoson and its total renal clearance values. Renal clearance decreased from 22.4 (L/h) in control group to 10.3, 7.3 and 2.3 L/h in mild, moderate and severe renal impairment groups, respectively. The exposure (AUC) increased from 11.7 ng-h/mL in control group to 28.2 ng-h/mL in severe renal impaired group. But the Cmax remains constant in normal, mild, moderate and severe impaired renal subjects. The side effects appear related to Cmax. The dose adjustment in renal impairment subjects is not necessary as the increase in HR is transient. The renal clearance of regadenoson in patients on hemodialysis was not evaluated. The influence of hepatic impairment on the pharmacokinetics of regadenoson was not evaluated.

The sponsor has studied the effect of 200-mg oral dose of caffeine on the regadenoson-induced increase in myocardial blood flow (MBF), measured approximately 2 hours after caffeine ingestion. The primary efficacy measure for this study was the log coronary flow reserve (CFR), which is the ratio of stress MBF after regadenoson dosing to the resting MBF and was determined by O-15 PET imaging. The primary efficacy analysis was to test whether caffeine reduces CFR after regadenoson administration by at least 10%. The log CFR ± SE for the placebo group (n=40) was 1.03 ± 0.06 and log CFR for the caffeine group (n=40) was 0.95 ± 0.06. The CFR (stress/rest) for the placebo group was 2.97 ± 0.16 and for the caffeine group was 2.75 ± 0.16. While there was no significant change in CFR, the study does not rule out nor does it establish a significant interaction between regadenoson and caffeine on log CFR.

Lexiscan was also evaluated in a randomized, double-blind, placebo-controlled, cross-over study in 24 subjects with mild and 24 subjects with moderate asthma who were responsive to challenge with adenosine monophosphate. Mean Forced Expiration Volume (FEV1) did not differ between lexiscan and placebo at any post-dosing measurement from 10 minnutes to 2 hours. The average peak drop in FEV1 was 5% after Lexiscan and 7% after placebo.

Lexiscan was also evaluated in a randomized, double-blind, placebo-controlled study in 38 subjects with moderate and 11 subjects with severe chronic obstructive pulmonary disease (COPD). The mean FEV1 did not differ between lexiscan and placebo at any post-dosing measurement from 10 min to 120 min. The incidence of broncho-constrictive response, defined as 15% reduction in FEV1 from baseline was 12% for lexiscan and 6% for placebo.

Aminophylline may be administered by slow intravenous injection (100 mg over 30-60 seconds) to attenuate sever and /or persistent adverse effects of Lexiscan.

## 2. Question Based Review

### 2.1 General Attributes of Drug

**What are the general attributes of the drug Lexiscan™ (regadenoson injection)?**

Lexiscan™ (Regadenoson Injection) is a pharmacologic stress agent to be used in conjunction with radionuclide myocardial perfusion imaging (MPI). Regadenoson is chemically described as adenosine, 2-[4-[(methylamino) carbonyl]-1H-pyrazol-1-yl]-, monohydrate. The molecular formula for regadenoson is $C_{15}H_{18}N_8O_5 \cdot H_2O$ and its molecular weight is 408.37. The chemical structure of drug substance is shown in Figure 1:

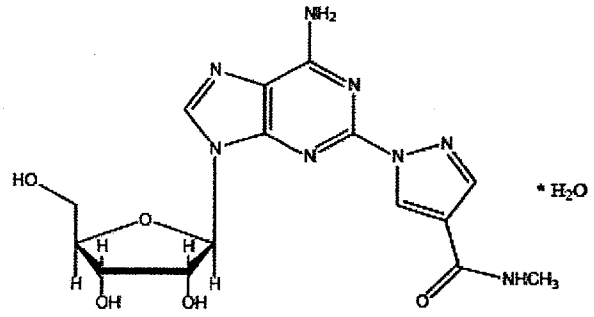



Figure 1. Chemical structure of regadenoson

**2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology of regadenoson?**

IND 62,862 was submitted to the Agency in June 2001 and the Division of Cardiovascular and Renal Products (DCRP) provided regulatory oversight and review responsibility for regadenoson through the completion of the Phase 3 program in August 2006. During development, meetings and teleconferences between the Sponsor and the Agency were held to discuss and reach agreement on the Chemistry, Pharmacology/Toxicology aspects of the program.

Responsibilities for the regadenoson IND were transferred from DCRP to the Division of Medical Imaging and Hematology Products (DMIHP) on September 1, 2006. The End of Phase 3 meetings were held with DMIHP in February 2007 confirming previous agreements on the development program.

### 2.1.2 What are the highlights of the chemistry and physico-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology review?

Regadenoson Injection 0.08 mg/mL consists of regadenoson, dibasic sodium phosphate, monobasic sodium phosphate, propylene glycol (PG), edetate disodium (EDTA), and water for injection, to be delivered in a 5 mL plastic syringe or 5 mL glass vial. The composition of drug product is shown in Table I:

Table I. Chemical composition of regedenoson

| Ingredient | Reference to Quality Standard | Function | Quantity (mg/mL) |
|---|---|---|---|
| Regadenoson | In-house standard | Active | 0.08[a] |
| Dibasic Sodium Phosphate, Dihydrate[b] | USP | [redacted] | 10.9 |
| Monobasic Sodium Phosphate, Monohydrate | USP | | 5.4 |
| Propylene Glycol | USP | | 150.0 |
| Edetate Disodium, Dihydrate | USP | | 1.0 |
| Water for Injection | USP | | q.s. |

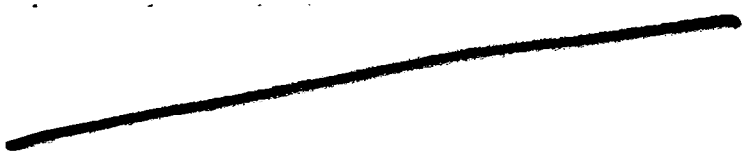
q.s. = quantity sufficient

[a] Concentration of regadenoson on anhydrous basis

[b] Alternatively, an equivalent amount (8.7 mg/mL) of Dibasic Sodium Phosphate, Anhydrous may be used in place of Dibasic Sodium Phosphate, Dihydrate.

Due to its low aqueous solubility, the solubility of regadenoson in several generally recognized as safe (GRAS) co-solvents and surfactants were investigated to achieve the appropriate concentrations of regadenoson in

solution. Based upon the dosing requirements, two formulation systems were developed: (1) a system containing methylboronic acid (MBA) formulated in used in nonclinical and early clinical studies; and (2) a system containing propylene glycol (PG) formulated in used in clinical and registration stability studies. The PG formulation uses EDTA as a



**2.1.4 What are the proposed dosage(s) and route of administration?**

Dose selection clinical studies were performed and a final dose of 0.4 mg regadenoson was selected. The Phase 3 clinical supplies using the PG formulation were manufactured at a regadenoson concentration of either 0.1 mg/mL (Study CVT 5131) or 0.08 mg/mL (Study CVT 5132). Final dose selection of 0.4 mg regadenoson for the Phase 3 studies occurred after manufacture of the first Phase 3 clinical batch at 0.1 mg/mL regadenoson. The 0.1 mg/mL formulation was diluted with vehicle prior to administration of the 5 mL dose volume. The 0.08 mg/mL concentration of regadenoson in the 15% PG formulation was chosen as the final clinical and commercial formulation, in order to deliver the dose in a 5 mL volume.

**2.1.5 What is the proposed mechanism of action of Regadenoson?**

Adenosine is a vasodilator of the coronary and peripheral circulation. The effect of adenosine to cause coronary and possibly peripheral vasodilation is mediated primarily by the A2a adenosine receptors present in vascular wall. Similarly, regadenoson is a selective A2a adenosine receptor agonist with at least 10-fold lower affinity for A1 and weak affinity, if any for A2b adenosine receptors. The sensitivity of the coronary circulation to adenosine and adenosine analogues appears to be greater than the peripheral vasculature. This differential sensitivity is likely, in part, due to a larger A2a

spare receptor capacity of coronary vessels relative to peripheral resistance vessels. The coronary vasodilator effect of regadenoson is the basis for its use, in conjunction with radionuclide MPI, to detect under perfused areas of myocardium. It causes a significantly increases (>2 fold) of CBF to myocardial areas perfused by normal, as opposed to stenotic, coronary arteries. Adenosine directly, and dipyridamole (an approved pharmacologic stressor) indirectly, activate all four known adenosine receptor subtypes designated A1, A2a, A2b, and A3 which mediate a variety of responses in different tissues.

## 2.2 General Clinical Pharmacology

There were eight clinical pharmacology studies performed by the sponsor. They are summarized in the table II:

Table II. Summary of clinical pharmacology studies performed to support NDA

| Study Number | Phase | Location of Study Centers (n) | Description | Number of Subjects/Patients Dosed with Regadenoson (dose) |
|---|---|---|---|---|
| CVT 5111 | 1 | United Kingdom (1) | Double-blind, randomized, placebo-controlled, crossover, dose-ranging, tolerability, safety and PK study in healthy male volunteers | 36 (0.1–30 μg/kg) |
| CVT 5112 | 1 | Germany (1) | Open-label PK and safety study in normal volunteers and renally impaired subjects | 24 (400 μg) |
| CVT 5121 | 2 | United States (4) | Open-label, dose-ranging, CBF response (Doppler flow wire), safety, and PK study in patients undergoing cardiac catheterization | 40 (10–500 μg) |
| CVT 5122 | 2 | United States (4) | Open-label, pilot radionuclide MPI efficacy, and safety study of two doses in patients indicated for pharmacologic stress MPI | 36 (400 μg: 18) (500 μg: 18) |
| CVT 5123 | 2 | Switzerland (1) | Double-blind, randomized, placebo-controlled, crossover study of caffeine interaction with regadenoson MBF response using positron emission tomography (PET) imaging in healthy volunteers | 43 (400 μg) |
| CVT 5124 | 2 | United Kingdom (1) | Double-blind, randomized, placebo-controlled, crossover study of $FEV_1$ (forced expiratory volume in the first second) response and safety in AMP-sensitive mild and moderate asthma subjects | 47 (400 μg) |
| CVT 5125 | 2 | United States (2) | Double-blind, randomized, placebo-controlled, crossover study of $FEV_1$ response and safety in moderate and severe COPD subjects | 49 (400 μg) |
| CVT 5126 | 2 | United States (3) | Double-blind, randomized, placebo-controlled, radionuclide MPI efficacy and safety study with low level exercise in patients indicated for pharmacologic stress MPI | 39 (400 μg) |

### 2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The clinical pharmacology studies included a Phase I, double-blind, randomized, placebo-controlled, dose-ranging, tolerability, safety and PK study in healthy volunteers; a Phase II open-label, dose-finding, coronary blood flow response (Doppler flow wire), safety and PK study in patients undergoing cardiac catheterization amongst others. The efficacy and safety of regadenoson was studied (and compared with Adenoscan) in two identical

randomized, double-blind studies in 2015 patients with known or suspected coronary artery disease. Each patient received an initial stress scan using adenoscan (6-minute infusion using a dose of 0.14 mg/kg/min, without exercise with one of the three radionuclide gated Single Photon Emission Computed Tomography (SPECT) imaging protocols. After the initial scan, patients were randomized to either regadenoson or Adenoscan, and received a second stress scan with the same radionuclide imaging protocol as that used for the initial scan. The median time between scan was 7 days. A 17-segment model was used, the number of segments showing a reversible perfusion defect was calculated for the initial adenoscan study and for the randomized study obtained using regadenoson or adenoscan. The agreement rate for the image obtained with regadenoson or adenoscan relative to the initial adenoscan category (0-1, 2-4, 5-17 reversible segments) were placed in the same category with the randomization scan. The studies demonstrated theat regadenoson is comparable to adenoscan in assessing the extent of reversible perfusion abnormalities.

2.2.2 **What is the basis for selecting the response endpoints, i.e. clinical or surrogate endpoints, or biomarkers (collectively called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?**

Average peak velocity (APV) measurements were performed by pulsed-wave Doppler ultrasonography. The primary efficacy variable (pharmacodynamic variable) was defined as the time (in seconds) that would yield a ratio of APV to baseline APV following administration of regadenoson of 2.0 or more. Doppler measurements of APV were recorded prior to adenosine challenge and during maximal hyperemia. If the study vessel responded to adenosine with a ratio of peak to baseline APV (coronary flow velocity reserve [CFR]) 2.5, the subject qualified for study inclusion. Prior to administration of regadenoson, another baseline Doppler measurement of APV was recorded. After administration of study drug, APV was continuously monitored and recorded until it returned to baseline or for 30 minutes post-dose, whichever occurred first. The evaluated doses of regadenoson that resulted in at least a 2-fold increase in mean APV from baseline for at least 2 minutes were 300, 400, and 500 µg. At the 400 µg and 500 µg doses, the effect was more sustained (magnitude and duration of response); peak flow was 2.5 times baseline for a median duration of 2.79

minutes and 2.85 minutes, respectively. 400 µg dose was therefore, chosen for Phase III clinical trials.

**2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?**

The assay used by the sponsor for the analysis of regadenoson (CVT-3146) in human plasma was HPLC/MS/MS method. The procedure involved extraction of regadenoson and the internal standard from human plasma by solid phase extraction, followed by analysis by high performance liquid chromatography coupled with mass spectrometry (LC/MS/MS) using positive-ion-spray ionization. The mass spectrometer was operated in the Multiple Reaction Monitoring (MRM) mode. The internal standard, [redacted] was used in the construction of standard calibration curves.

Quantitation in human plasma was based on peak area ratios from the response of the analyte to the internal standard, referenced to duplicate ten point standard calibration curves. All sample concentrations were calculated using a linear regression with 1/x weighting (where x is the concentration of a given calibration standard). The intra-day and inter-day accuracy and precision for regadenoson samples in heparinized human plasma was acceptable and ranged from 0.04-40.0 ng/mL. A similar method was used to determine regadenoson concentration in human urine samples as well.

**2.2.4 Exposure-Response Evaluation**

**2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.**

A Phase II, open-label, single-dose study in subjects undergoing a clinically indicated cardiac catheterization was performed. A dose-escalation study, evaluating up to five dose levels: 30, 100, 300, 600, and 900 µg regadenoson until a dose was identified that increased average peak velocity (APV) to twice the baseline level for at least 2 minutes and that was well tolerated. APV measurements were performed by Pulsed-wave Doppler

ultrasonography. Dose escalation was to proceed only if lower doses were tolerated and APV data suggested that escalation was investigationally necessary. Intermediate doses were to be studied to adequately describe the dose-response relationship, as necessary. On the day of the study, and prior to administration of regadenoson, baseline laboratory tests and a coronary angiography were performed; during the angiography, a study vessel was selected (left anterior descending coronary artery [LAD] or left circumflex coronary artery [LCx]) and study eligibility was confirmed (= 50% stenosis in LAD or LCx, no severe coronary stenosis [= 70% diameter reduction unless vessel had a widely patent graft], no aortic stenosis with valve area < 1.5 $cm^2$, no obstructive cardiomyopathy). The selected study vessel (LAD or LCx) was challenged by up to three intracoronary (IC) injections of 18 µg adenosine. Doppler measurements of APV were recorded prior to adenosine challenge and during maximal hyperemia. If the study vessel responded to adenosine with a ratio of peak to baseline APV (coronary flow velocity reserve [CFR]) = 2.5, the subject qualified for study inclusion. Prior to administration of regadenoson, another baseline Doppler measurement of APV was recorded. After administration of study drug, APV was continuously monitored and recorded until it returned to baseline or for 30 minutes post-dose, whichever occurred first. The primary efficacy variable (Part A) was defined as the time (in seconds) that the ratio of APV to baseline APV following administration of regadenoson was at least 2.0. Other APV measures included: (1) the ratio of peak APV to baseline APV, (2) the time of peak APV, (3) the time of near-peak APV (APV = 85% of peak), (4) the ratio of APV to baseline APV, and (5) the ratio of peak APV to baseline APV, expressed as a percentage of CFR.

The evaluated doses of regadenoson that resulted in at least a 2-fold increase in mean APV from baseline for at least 2 minutes were 300, 400, and 500 µg. At the 400 µg and 500 µg doses, the effect was more sustained in terms of magnitude and duration of response; peak flow was 2.5 times baseline for a median duration of 2.79 minutes and 2.85 minutes, respectively. A 400 µg dose was therefore, chosen for Phase III clinical trials.

**2.2.4.2 Does this drug prolong the QT or QTc interval?**

Regadenoson does cause a transient increase in QTc. The adverse events reflected the pharmacological effect of the drug and were related to vasodilation and an increase in HR. The most frequently reported drug-

related adverse events included palpitation, vasodilation, dizziness, and ECG T-wave inversion.

ECG abnormalities were clinically significant (T-wave inversion and ST segment depression), occurred only after dosing with regadenoson. Generally, these abnormalities occurred at 3.0 μg/kg dose level and were most frequent at the 20.0 μg/kg dose level. ECG abnormalities occurred within 1.2 min of dosing and resolved within a few (15-60) minutes.

**2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?**

The dose and dosing regimen selected by the sponsor is consistent with the known relationship between dose-concentration-response. There are no unresolved dosing or administration issues.

**2.2.5 Pharmacokinetic Characteristics**

**2.2.5.1 What are the PK characteristics of the drug and its major metabolites?**

A Phase I, double blind, randomized, placebo-controlled, crossover ascending single intravenous (IV) bolus dose study was conducted to support safety and PK in healthy volunteers. Escalating doses of regadenoson were evaluated until a maximum tolerated dose (MTD) was achieved. The doses evaluated were 0.1, 0.3, 1.0, 3.0, 10.0, 20.0, 30.0, 40.0 and 50 μg/kg. Placebo was chosen as the control treatment to avoid bias in the study and to observe if any effects were treatment related.
Peak plasma regadenoson concentrations were attained rapidly following dosing, with Tmax(obs) observed between 0.017 and 0.067 h postdose. Following Tmax(obs), there was evidence of a multi-exponential decline. Terminal elimination half life ($t_{½el}$) ranged between 1.41 to 4.09 hours across all subjects. Clearance exhibited a similar level of variability ranging from 263.5 to 890.4 ml/h. Systemic exposure (AUC(0-t) and AUC(0-inf)) increased in proportion to the dose. In addition, increases in Cmax were largely proportional across the entire dose range from 0.1 to 20.0 μg/kg. As the dose increased further to 30.0 μg/kg there was a suggestion of a less than proportional increase (Figure 2 and Figure 3). Mean AUC(0-inf) estimates increased in the ratio 1 (0.3 μg/kg): 2.5 (1.0 μg/kg): 8.6 (3.0 μg/kg): 25 (10.0

μg/kg): 53.6 (20.0 μg/kg): 62.8 (30.0 μg/kg), with mean estimates of 0.67, 1.65, 5.72, 16.6, 35.7 and 41.8 ng/h/mL, respectively.

Renal excretion of unchanged drug amounted to on average 57% with no relationship to the dose administered. No consistent effect of dose was apparent in CL estimates obtained for doses between 0.3 and 20.0 μg/kg. However, as the dose increased to 30.0 μg/kg a slight increase of CL was observed, probably due to saturated renal reabsorption. The mean clearance estimates were 517, 613, 526, 610, 577 and 730 mL/h/kg for the 0.3, 1.0, 3.0, 10.0, 20.0 and 30.0 μg/kg doses, respectively.

It is not known whether regadenoson is metabolized in humans. Incubation with rat, dog, and human liver microsomes as well as human hepatocytes produced no detectable metabolites of regadenoson. Following intravenous administration of $^{14}$C-radiolabeled regadenoson to rats and dogs, about 90% of the dose was recovered in 24-48 hours in urine and feces (37% and 54%, respectively, in both species). Most of the radioactivity (87-95%) was recovered as unchanged regadenoson. These finding imply that metabolism of regadenoson does not play a major role in the elimination of the drug.

In healthy volunteers, 57% of the regadenoson dose is excreted unchanged in the urine (range 19-77%), with an average plasma renal clearance around 450 mL/min, i.e. in excess of glomerular filteration rate. This indicates renal tubular excretion plays a role in regadenoson elimination.

## 2.3 Intrinsic factors

### 2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response and what is the impact of any differences in exposure on efficacy or safety responses?

Renal function had a pronounced effect on renal clearance of regadenoson and its total renal clearance values. Renal clearance decreased from 22.4 (L/h) in control group to 10.3, 7.3 and 2.3 L/h in mild, moderate and severe renal impairment groups, respectively. The exposure (AUC) increased from 11.7 ng-h/mL in control group to 28.2 ng-h/mL in severe renal impaired group. As expected, the biological half-life increased from 2.0 h (control group) to 3.7 for severe renal impaired group. The administration of

regadenoson was associated with a rapid increase in heart rate in all our treatment groups. The mean increase from baseline was greatest at 2 min postdose, returning to within 10 bpm of baseline after 15-60 min. tachycardia was frequently reported as an adverse event. At 2 min after the regadenoson bolus, all four treatment groups showed a mean increase in QTc that resolved by 15 to 30 minute time point.

There was no relationship between weight and exposure of drug. The impact of race and gender on exposure was not evaluated.

**2.3.2 Based upon what is known about exposure-response relationships and their variability, and the groups studied, healthy volunteers vs patients vs. specific population, what dosage regimen adjustments, if any, are recommended for which of these groups?**

The sponsor conducted a study to investigate the relationship between renal function and regadenoson clearance. Kidney function had a pronounced effect on regadenoson clearance. The renal clearance decreased from 22.4 L/h in control group to 10.3, 7.3, and 2.3 L/h in mild, moderate and severe renal impaired subjects, respectively. As expected, the exposure went up from 11.1 ng-h/mL in normal control to 28.2 ng-h/mL for patients with severe renal impairment. No dose adjustment is necessary, however, as regadenoson is going to be administered only one time and side-effects are Cmax related and transient in nature.

## 2.4 Extrinsic Factors

**2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose- exposure and/or response and what is the impact of any differences in exposure on response?**

The sponsor has studied the effect of 200-mg oral dose of caffeineon the regadenoson-induced increase in myocardial blood flow (MBF), measured approximately 2 hours after caffeine ingestion. The sponsor also evaluated regadenoson-induced heart rate (HR) response with and without caffeine and also evaluated the relationship between the regadenoson-induced MBF and HR and BP, and whether they are altered by oral caffeine.

The primary efficacy measure was the log coronary flow reserve (CFR), which is the ratio of stress MBF after regadenoson dosing to the resting MBF and was determined by O-15 PET imaging. The primary efficacy analysis was to test whether caffeine reduces CFR after regadenoson administration by at least 10%. The log CFR ± SE for the placebo group (n=40) was 1.03 ± 0.06 and log CFR for the caffeine group (n=40) was 0.95 ± 0.06. The CFR (stress/rest) for the placebo group was 2.97 ± 0.16 and for the caffeine group was 2.75 ± 0.16. While there was no significant change in CFR detected in this study, the study does not rule out nor does it establish a significant interaction between regadenoson and caffeine on log CFR. The exponentiated upper and lower limits of the 95 and 90% confidence intervals for log CFR (caffeine versus placebo difference) are 1.08 and 0.78 and 1.06 and 0.80, respectively. Since this lower limit is less than 0.9, but the upper limit is > 1, this study cannot establish or rule out an interaction. However, there is 95% confidence that the change in CFR is not greater than 20%.

### 2.4.2 Is regadenoson safe to be used in patients with moderate and severe (stage 1 and stage 2) chronic obstructive pulmonary disease (COPD)?

Patients with bronchoconstrictive disease were excluded from clinical trials. Regadenson was generally well tolerated in non-MPI, placebo-controlled studies in subjects with mild to moderate asthma or moderate to severe COPD. However, FEV1 reductions of greater than 15% were observed in some subjects after receiving regadenoson or after receiving placebo.

### 2.4.3 Drug-Drug Interactions

No formal pharmacokinetic drug-drug interaction studies were conducted.

### 2.4 General Biopharmaceutics:

Not applicable

13 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Clin Pharm/Bio-* 9

# 4. APPENDICES:

## 4.1 Proposed Package Insert (Original and Annotated)

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*Withheld Track Number: Clin Pharm/Bio-* 10

## 4.2 INDIVIDUAL STUDY REVIEW:

STUDY 5111:

Study 5111 was a Phase I, double blind, randomized, placebo-controlled, crossover ascending ingle intravenous (IV) bolus dose study. Escalating doses of regadenoson were to be evaluated until a maximum tolerated dose (MTD) was achieved. The doses evaluated were 0.1, 0.3, 1.0, 3.0, 10.0, 20.0, 30.0, 40.0 and 50 µg/kg. Placebo was chosen as the control treatment to avoid bias in the study and to observe if any effects were treatment related. No PD was recorded for this study.

Doses were administered in ascending manner following safety review of previous dose. Each of the nine dose levels was to include 4 volunteers; each of the four volunteers was assigned to four treatment sequences as follows:

| Sequence | Supine | | Standing | |
|---|---|---|---|---|
| 1 | Active | Placebo | Active | Placebo |
| 2 | Active | Placebo | Placebo | Active |
| 3 | Placebo | Active | Active | Placebo |
| 4 | Placebo | Active | Placebo | Active |

Treatment period comprised of Days -1, 1, 2, 3, 4 and 5. Dosing occurred as single IV bolus (injected in 20 min) administered on Day 1 and Day 2 while supine and IV injection while standing on Day 3 and 4.

Dose justification:

IV route was chosen as the intended route of administration for subjects. A bolus dose given over 20 sec enabled both a rapid onset of effect and a rapid return to baseline conditions. Studies on awake dog showed an increase in coronary blood flow after short bolus of regadenoson given over 10 sec, with an ED50 dose of 0.34 µg/kg. A bolus of 1 µg/kg to anesthetized dog caused a transient maximal drop in mean arterial pressure of 17.5 mm Hg and a maximal increase in heart rate (HR) of 140 bpm to 150 bpm. Effect of blood pressure (BP) and HR in toxicology studies on the dog were seen at doses from 20 µg/kg given over 3-5 min, but not after 10 µg/kg. Allometric scaling of PK parameters for regadenoson in the rat and dog indicated that volume

of distribution and clearance in man would have been relatively similar to the dog when adjusted for body weight. It was therefore, predicted that some effects on coronary blood flow may start to occur in the range of 0.3 to 1.0 µg/kg.

Based on this data, the starting dose was selected to be 0.1 µg/kg, which is at least 10 times below the dose where effects on systemic BP and HR were predicted to start to be seen. The highest dose was 20.0 µg/kg, which is 120 times lower than a dose shown to be safe in acute toxicology study in dog. Because an MTD was not achieved with regadenoson doses up to 20 µg/kg in this study, protocol was amended to evaluate doses up to 50 µg/kg (48 times lower than a dose shown to be safe in an acute toxicology study in dogs).

Thirty-six subjects were planned, 4 at each of 9 dose level, 4 at each level were dosed. A total of 36 analyzed, 4 at each of 5 dose levels: 0.1, 1.0, 3.0, 10.0 and 30 µg/kg and 8 at each of 2 dose levels: 0.3 and 20.0 µg/kg. No subject was dosed at 40.0 and 50.0 µg/kg dose levels.

PK Results:

Peak plasma regadenoson concentrations were attained rapidly following dosing, with Tmax(obs) observed between 0.017 and 0.067 h postdose throughout. Following Tmax(obs), there was evidence of a multi-exponential decline in all profiles.

Terminal elimination half life ($t_{½el}$) was moderately consistent, ranging between 1.41 to 4.09 hours across all subjects (Table III). Clearance exhibited a similar level of variability ranging from 263.5 to 890.4 ml/h. Peak plasma concentrations of regadenoson were attained rapidly and thereafter there was evidence of multi-exponential decline. Systemic exposure (AUC(0-t) and AUC0-inf) increased in proportion to the dose. In addition, increases in Cmax were largely proportional across the entire dose range from 0.1 to 30.0 µg/kg. Terminal elimination half-life estimates were comparable for all doses (with mean ranging from 1.8 to 2.3 h). Renal excretion of unchanged drug amounted to on average 57% with no relationship to the dose administered. No consistent effect of dose was apparent in CL estimates obtained for doses between 0.3 and 20.0 µg/kg. However, as the dose increased o 30.0 µg/kg a slight increase was observed, probably due to saturated renal absorption. The mean clearance estimates

were 517, 613, 526, 610, 577 and 730 mL/h/kg for the 0.3, 1.0, 3.0, 10.0, 20.0 and 30.0 µg/kg doses, respectively.

Estimates indicative of systemic exposure (AUC(0-t) and AUC(0-inf)) exhibited a broadly dose proportional increase between doses of 0.3 and 20.0 µg/kg (Table IV). As the dose increased further to 30.0 µg/kg there was a suggestion of a less than proportional increase (Figure 2 and Figure 3). Mean AUC(0-8) estimates increased in the ratio 1 (0.3 µg/kg): 2.5 (1.0 µg/kg): 8.6 (3.0 µg/kg): 25 (10.0 µg/kg): 53.6 (20.0 µg/kg): 62.8 (30.0 µg/kg), with mean estimates of 0.67, 1.65, 5.72, 16.6, 35.7 and 41.8 ng/h/mL, respectively. Cmax(obs) also exhibited a largely dose proportional increase between 0.1 and 30 µg/kg (mean Cmax(obs) estimates were 0.39, 1.80, 6.04, 12.13, 39.18, 102.0 and 133.5 ng/mL for the 0.1, 0.3, 1.0, 3.0, 10.0, 20.0 and 30.0 µg/kg doses, respectively).

Estimates of terminal elimination half life (t½el) were comparable across all doses, with mean estimates ranging from 1.853 to 2.308 h throughout. No consistent effect of dose was apparent in CL estimates obtained for doses between 0.3 and 20.0 µg/kg; however, as the dose increased to 30.0 µg/kg a slight increase was observed, likely due to saturated renal re-absorbtion. This reflected the apparent dose proportionality in AUC(0-inf) observed at doses up to 20.0 µg/kg and the slightly sub-proportional increase as the dose increased further to 30.0 µg/kg (Table IV) (mean clearance estimates were 517, 613, 526, 610, 577 and 730 mL/h/kg for the 0.3, 1.0, 3.0, 10.0, 20.0 and 30.0 µg/kg doses, respectively). The great majority of the drug was cleared within 12 h after dose administration, with concentrations below LOQ at 24 h. The urine collection over 24 h after dose had therefore been considered complete with respect to drug excretion. The fraction of administered dose that was recovered unchanged in urine was on average 0.57, ranging from 0.19 to 0.77.

Table III. $T_{1/2\ El}$ (h) for all subjects dosed with regadenoson in supine phase

| Dose Level | SUPINE Mean | Median | SD | Min | Max | N |
|---|---|---|---|---|---|---|
| 0.1 µg/kg | - | - | - | | | 0 |
| 0.3 µg/kg | 2.308 | 1.530 | 1.290 | | | 6 |
| 1.0 µg/kg | 1.870 | 1.895 | 0.286 | | | 4 |
| 3.0 µg/kg | 2.138 | 2.170 | 0.212 | | | 4 |
| 10.0 µg/kg | 2.203 | 2.270 | 0.166 | | | 4 |
| 20.0 µg/kg | 1.974 | 1.940 | 0.281 | | | 8 |
| 30.0 µg/kg | 1.853 | 1.836 | 0.219 | | | 4 |

Table IV. AUC(0-α) in ng-h/ml for all subjects dosed with regadenoson in supine phase

| Dose Level | SUPINE Mean | Geometric Mean | Median | SD | CV (%) | Min | Max | N |
|---|---|---|---|---|---|---|---|---|
| 0.1 µg/kg | - | - | - | - | - | - | - | 0 |
| 0.3 µg/kg | 0.66573 | 0.61827 | 0.52490 | 0.29554 | 42.7 | | | 6 |
| 1.0 µg/kg | 1.6450 | 1.6383 | 1.6490 | 0.17093 | 10.5 | | | 4 |
| 3.0 µg/kg | 5.7155 | 5.7119 | 5.7690 | 0.23260 | 4.1 | | | 4 |
| 10.0 µg/kg | 16.622 | 16.505 | 16.215 | 2.3154 | 13.8 | | | 4 |
| 20.0 µg/kg | 35.712 | 35.170 | 34.105 | 6.8325 | 18.7 | | | 8 |
| 30.0 µg/kg | 41.778 | 41.431 | 42.550 | 6.0670 | 15.2 | | | 4 |

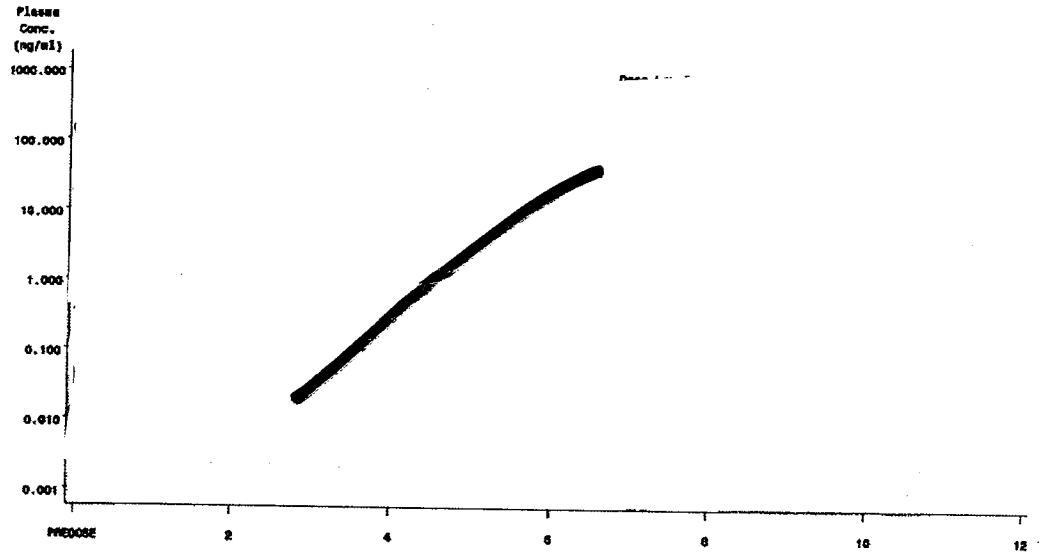
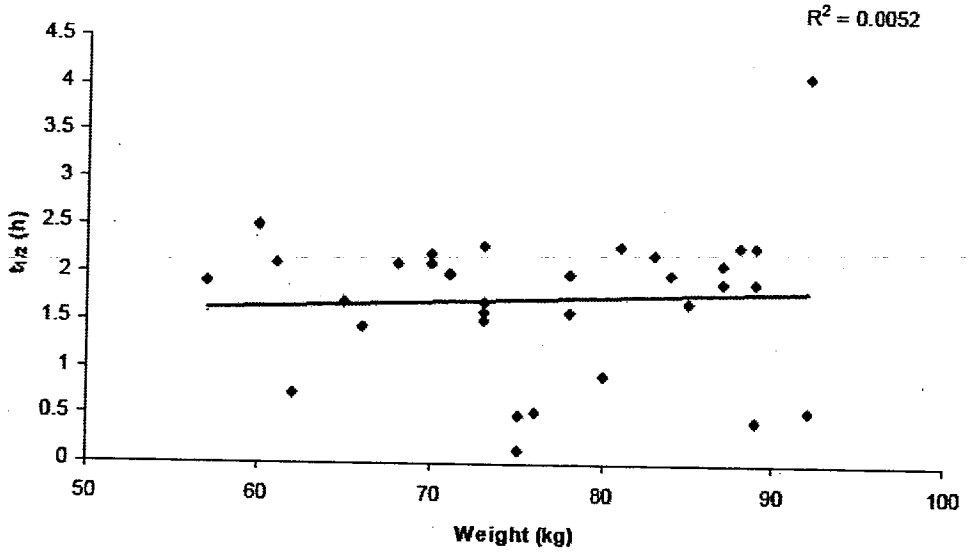



Figure 2. Plasma concentration (ng/mL) with time on a logarithmic scale

Half-Life Vs Weight and Clearance Vs Weight:

The half-life and clearance of regadenoson were evaluated with respect to weight. There was no effect of weight on half-life. However, there was a slight change (increase) in clearance of regadenoson with increase in weight (Figure 3).



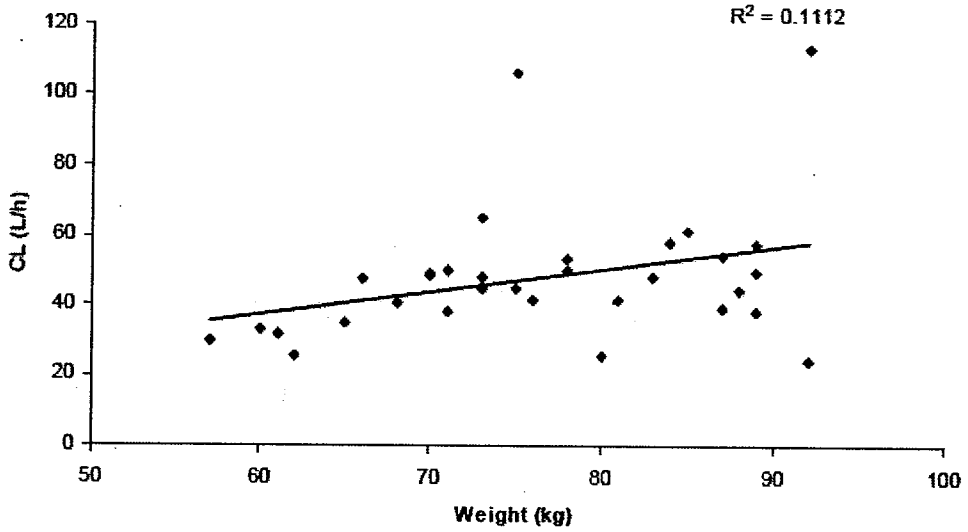



Figure 3. The correlation of weight with half-life and clearance of regadenoson

Safety (Study 5111):

The number and severity of adverse events increased with increasing dose of regadenoson. In general, adverse events reflected the pharmacological effect of the drug and were related to vasodilation and an increase in HR. The most frequently reported drug-related adverse events included palpitation, vasodilation, dizziness, and ECG T-wave inversion. Adverse events were generally assessed as mild or moderate; however, 3 subjects experienced a severe adverse event: dizziness and syncope, each experienced by one subject following a 20.0 µg/kg (standing) dose of regadenoson, and palpitation, experienced by one subject following regadenoson 30.0 µg/kg (supine). The majority of adverse events started within 1-2 min after dosing and lasted only a few minutes (the majority < 10 min), resolving spontaneously.

Based on the adverse event profile in this study, the MTD for iv regadenoson was 10.0 µg/kg after administration in the standing position and 20.0 µg/kg in the supine position. At dose levels of = 1.0 µg/kg of regadenoson (in both supine and standing positions) a marked increase in HR occurred within 1.2 min after dosing and lasted for several minutes. The magnitude and duration of the increase in HR increased with increasing dose of regadenoson (Table V). The maximal effect was observed at the 20.0

Table V. Mean Maximum heart rate increase in supine position after regadenoson administration

| Supine Position | Regadenoson Dose | | | | | | |
|---|---|---|---|---|---|---|---|
| | 0.1 µg/kg (n = 4) | 0.3 µg/kg (n = 8) | 1.0 µg/kg (n = 4) | 3.0 µg/kg (n = 4) | 10.0 µg/kg (n = 4) | 20.0 µg/kg (n = 8) | 30.0 µg/kg (n = 4)* |
| **Placebo** | | | | | | | |
| Mean baseline HR (bpm) | 71 | 69 | 68 | 65 | 70 | 67 | 70 |
| Maximum increase from baseline (bpm) | 3 | 0 | 2 | 1 | 2 | 3 | 4 |
| % Increase over baseline | 4% | 0 | 3% | 2% | 3% | 5% | 6% |
| Time of maximum increase postdose | 2 min | 1 min | 1 min | 10 min | 1 min | 7 min | 1 min |
| Duration of increase if ≥ 15 bpm over baseline value | NA | NA | NA | NA | NA | NA | NA |
| **Regadenoson** | | | | | | | |
| Mean baseline HR (bpm) | 72 | 66 | 71 | 65 | 71 | 69 | 80 |
| Maximum increase from baseline (bpm) | 1 | 14 | 25 | 39 | 51 | 58 | 62 |
| % Increase over baseline | 1% | 21% | 35% | 60% | 72% | 84% | 78% |
| Time of maximum increase postdose | 1 min | 4 min | 1 min | 1 min | 2 min | 3 min | 3 min |
| Duration of increase if ≥ 15 bpm over baseline value | NA | NA | 2 min | 7 min | 20 min | 45 min | 45 min |

µg/kg (supine and standing) and 30.0 µg/kg (supine) dose levels where a > 70% mean increase from baseline HR was observed, with the HR returning to within 15 bpm of baseline after 45 min (supine) and 20 min (standing).

After regadenoson dosing, there were transient changes in BP (with both increases and decreases in SBP and DBP). After administration in the standing position, 5 subjects with significant decreases in SBP were symptomatic, with 1 subject experiencing severe syncope (Table VI). There were no clinically significant changes from baseline in hematology, clinical chemistry, or urinalysis values in any subject after dosing with regadenoson.

ECG abnormalities, assessed by the investigators as clinically significant (T-wave inversion and ST segment depression), occurred only after dosing with regadenoson. Generally, these abnormalities occurred at dose levels = 3.0 µg/kg and were most frequent at the 20.0 µg/kg dose level. ECG abnormalities occurred within 1.2 min of dosing and resolved within a few minutes.

With regard to the centralized ECG reading laboratory evaluation, there was no clinically significant or dose-dependent change from baseline in either mean QRS duration or QT dispersion. QT and RR interval data for the

supine placebo period were pooled across subjects to determine the optimal heart rate correction factor based on the generic formula $QTc = QT/RR^{\alpha}$. The value of $\alpha$, minimizing the correlation between QTc and HR, was 0.267. QTc values after administration of active regadenoson, calculated using this formula, showed no increase from the placebo values at corresponding time points.

Table VI. Summary of subjects with substantial changes in vital sign within 20 minutes after regadenoson injection

| | Placebo | 0.1 µg/kg | 0.3 µg/kg | 1.0 µg/kg | 3.0 µg/kg | 10.0 µg/kg | 20.0 µg/kg | 30.0 µg/kg |
|---|---|---|---|---|---|---|---|---|
| Supine | (n=35) | (n=4) | (n=8) | (n=4) | (n=4) | (n=4) | (n=8) | (n=4) |
| SBP (± 20 mm Hg change) | 0 | 0 | 0 | 0 | 2 (50%) | 2 (50%) | 2 (25%) | 2 (50%) |
| DBP (± 20 mm Hg change) | 0 | 0 | 0 | 0 | 0 | 1 (25%) | 2 (25%) | 2 (50%) |
| HR (± 15 bpm change) | 0 | 0 | 0 | 0 | 4 (100%) | 4 (100%) | 8 (100%) | 4 (100%) |
| Standing | (n=24) | (n=4) | (n=4) | (n=4) | (n=4) | (n=4) | (n=4) | NA[a] |
| SBP (± 20 mm Hg change) | 0 | 0 | 1 (25%) | 1 (25%) | 1 (25%) | 1 (25%) | 3 (75%) | – |
| DBP (± 20 mm Hg change) | 0 | 0 | 0 | 1 (25%) | 0 | 2 (50%) | 2 (50%) | – |
| HR (± 15 bpm change) | 1 (4%) | 2 (50%) | 1 (25%) | 2 (50%) | 3 (75%) | 3 (75%) | 4 (100%) | – |

[a] No subjects were dosed.

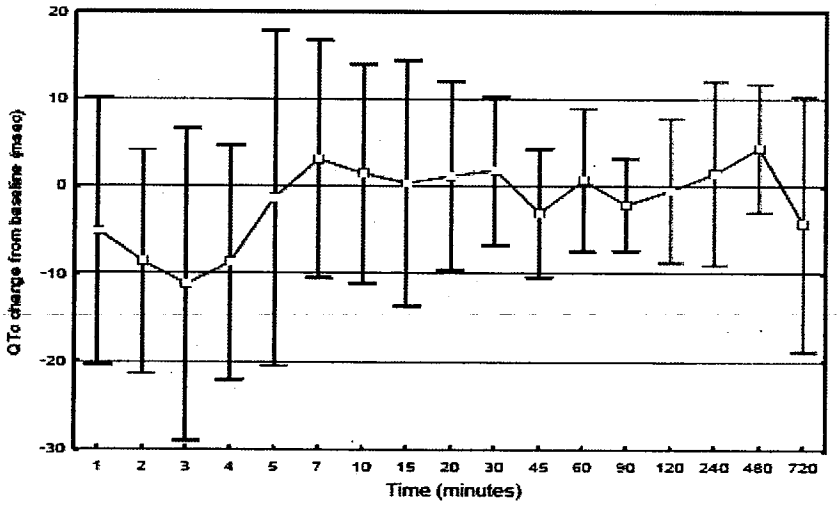



Figure 4. Change in QTc from baseline with time in a 20 µg/kg dose group

Overall Conclusion:
The maximum tolerated dose of regadenoson was determined to be 10 µg/kg in the standing position and 20 µg/kg in the supine position. Dose limiting

events were consistent with those expected of a selective adenosine A2A agonist including vasodilation, dizziness and increases in heart rate. Regadenoson administration had no effect on the QTc interval and no consistent effects on blood pressure. Peak concentrations of regadenoson were attained rapidly after dosing with a multi-exponential decline thereafter. Over the dose range 0.1 to 20 μg/kg Cmax and AUC generally increased in proportion to dose.

STUDY 5112:

The primary objective of this study was to investigate the relationship between renal function and regadenoson clearance. The secondary objectives were to investigate the effect of decreased function on other pharmaco-kinetic factors such as volume of distribution, elimination half-life and to evaluate whether regadenoson affect renal function in subjects with renal impairment.

This study was an open-label, single-dose study of regadenoson in normal subjects and subjects with renal insufficiency (mild, moderate, and severely impaired). Each subject received a single 400 μg/kg IV dose of regadenoson, administered over 10 sec, followed by 5 mL saline flush. Blood and urine samples were collected and measures of safety collected until 36 hours after administration of drug.

**Number of Subjects (Planned and Analyzed)**: Twenty-four male and female subjects (four groups of six subjects each) were planned. Six subjects with normal renal function and seven subjects with mild, six subjects with moderate, and five subjects with severe renal impairment were enrolled and completed the study.

**Diagnosis and Main Criteria for Inclusion**: Adult men or women (= 18 years of age) who provided written informed consent, and who had creatinine clearance values in the following ranges: normal renal function (CLCR of 80 to 140 mL/min), mild renal impairment (CLCR at least 50 but less than 80 mL/min), moderate renal impairment (CLCR at least 30 but less than 50 mL/min), and severe renal impairment (CLCR of less than 30 mL/min), were considered for inclusion in the study. Enrolled subjects were to have had no change in renal function in the previous 2 months, and no clinically relevant physical findings, laboratory abnormalities, ECG findings, or vital signs at screening, except for those related to impaired

renal function. Subjects were required to be nonsmokers or to smoke no more than 10 cigarettes per day. They were also required to abstain from intake of caffeine or other methylxanthines during the study. Female subjects must have been postmenopausal or, if of child bearing potential, must have had negative screening and baseline pregnancy tests and have used an acceptable method of birth.

Subjects were not eligible for enrollment in the study if they had concurrent illness requiring ongoing treatment (except controlled hypertension, diabetes, and renal impairment, for renal impaired subjects), or if they had any medical condition that might interfere with the pharmacokinetics of regadenoson (except renal impairment in renally impaired subjects). Those requiring dialysis and those who had donated or lost more than 300 mL of blood/plasma in the past 12 weeks or who intended to donate blood within 1 month of study completion were excluded from the study. Those with a history of congestive heart failure or ejection fraction = 35%, or a history of bronchoconstrictive and bronchospastic lung disease were not permitted to enroll. Subjects with a screening hemoglobin value below 9 g/dL; a positive HIV test; known serum hepatitis or carriers of the hepatitis B surface antigen (HbsAg) or the hepatitis C antibody; or with hyperkalemia or hypokalemia together with any of the following ECG changes (peaked or tented T wave, second- or third-degree AV block, QRS widening, biphasic wave QRS and T fusion, or imminent ventricular standstill) were not enrolled. In addition, subjects with a history of serious uncontrolled ventricular arrhythmia, or those with a history of greater than first-degree AV block or current sick sinus syndrome without a functioning artificial pacemaker, were not eligible for enrollment. A history of drug or alcohol abuse, or a positive drug screen or positive alcohol breath test ruled out study enrollment. Subjects currently taking theophylline or aminophylline or having a known allergy to either medication were prohibited from entering the study.

**Test Product, Dose, Mode of Administration, Batch Number:**
Open-label study drug was supplied as sterile stock solution in single-use vials each containing 5 mL of regadenoson (0.08 mg/mL). Study personnel placed a peripheral IV catheter in the study subject, then administered a rapid bolus of the regadenoson solution (approximately 10 seconds) into the IV, followed immediately by a 5 mL saline flush. Study drug had the following CVT lot number 903604.

**Pharmacokinetics and Pharmacodynamics**: The following pharmacokinetic (PK) parameters for regadenoson were calculated using non-compartmental methods: maximum plasma concentration (Cmax), area under the concentration-time curve from time of administration to the last measurable sample (AUC0-t) or to infinity (AUC0-∞), regadenoson total clearance (CL), renal clearance (CLR), volume of distribution at steady state (Vss), elimination rate constant (kel), elimination half-life (t½), the fraction of regadenoson excreted unchanged (fe) in urine, and the volume of the unbound fraction.

Regadenoson plasma concentrations exhibited a tri-exponential decline in plasma concentrations after bolus dosing, with rapid distribution phases and a somewhat slower elimination phase. Kidney function had a pronounced effect on the renal clearance of regadenoson and its total renal clearance values. With decreasing $CL_{CR}$, the fraction of regadenoson excreted unchanged in urine decreased and elimination half-life increased, resulting in decreased CL and increased AUC values (Table VII). The type and frequency of adverse events experienced by subjects in this study were similar in the various renal impairment groups, and included tachycardia, flushing, headache, dizziness, chest discomfort, QTc interval prolongation, palpitation, and nausea. Adverse events were generally mild or moderate, started within 5 min after dosing, lasted less than 30 min, and resolved spontaneously. There were no adverse events that appeared to become more frequent with increasing severity of renal impairment. There were no clinically significant changes from baseline in mean or individual serum creatinine levels following treatment with regadenoson, suggesting that regadenoson does not affect renal function in patients with or without renal impairment. Administration of regadenoson was associated with a rapid increase in heart rate in all four treatment groups, returning to within 10 bpm of baseline in 15–60 min. Regadenoson effects on blood pressure were generally small.

All four renal impairment groups showed a mean increase in QTc at 2 min that resolved by the 15 and 60 min time points. The observed transient increase in QTc after regadenoson administration could be attributed to the momentary increase in heart rate with a delay in QT adaptation (hysteresis).

Table VII. PK parameters for regadenoson estimated from non-compartmental analysis in renal impairment group.

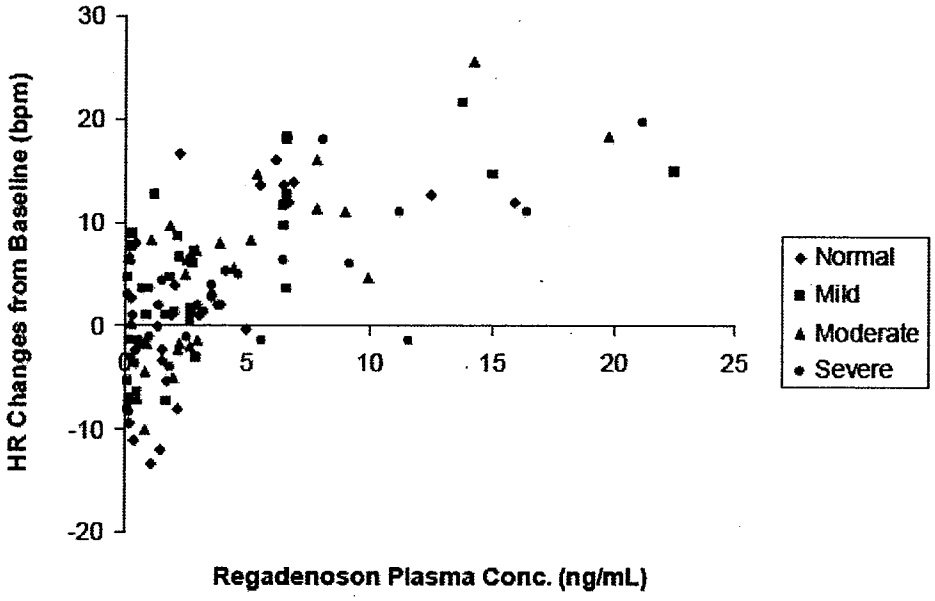
| Parameter Mean (SD) | Renal Impairment Group | | | |
|---|---|---|---|---|
| | None (n = 6) | Mild (n = 7) | Moderate (n = 6) | Severe (n = 5) |
| $C_{max}$ (ng/mL) | 13.62 (1.3) | 15.84 (3.2) | 15.64 (3.3) | 17.52 (3.5) |
| $AUC_{0-t}$ | 11.1 (1.4) | 15.8 (4.2) | 20.2 (6.3) | 27.0 (5.4) |
| $AUC_{0-\infty}$ | 11.7 (1.6) | 16.4 (4.4) | 21.5 (7.0) | 28.2 (5.3) |
| CL (L/h) | 35 (5.7) | 26 (6.6) | 20 (5.4) | 15 (2.7) |
| $V_{SS}$ (L) | 74.5 (8.9) | 64.9 (11.9) | 66.9 (10.3) | 63.4 (13.9) |
| $k_{el}$ | 0.35 (0.0) | 0.29 (0.1) | 0.24 (0.0) | 0.20 (0.1) |
| $t_{1/2}$ (h) | 2.0 (0.3) | 2.4 (0.4) | 2.9 (0.4) | 3.7 (1.1) |
| $f_e$ | 0.65 (0.1) | 0.41 (0.1) | 0.36 (0.1) | 0.16 (0.1) |
| $CL_R$ (L/h) | 22.4 (1.8) | 10.3 (3.2) | 7.3 (4.0) | 2.3 (1.0) |
| Volume of unbound fraction (L) | 110.5 (11.2) | 89.5 (14.1) | 93.1 (17.0) | 91.8 (20.2) |

Safety:

The administration of regadenoson was associated with a rapid increase in heart rate in all four treatment groups (Figure V). The mean increase from baseline was greatest at 2 min postdose, returning to within 10 bpm of baseline after approximately 15-60 min. tachycardia was frequently reported as an adverse event. A small transient increase in mean supine systolic blood pressure was observed immediately after regadenoson administration, but there were no clear early effects on systolic standing blood pressure or diastolic blood pressure. At 12 h postdose, all renal impairment groups had a transient increase in supine and standing systolic blood pressure, and the moderate and severe groups also had a transient increase in supine and standing systolic blood pressure. At 2 min after the regadenoson bolus, all four treatment groups showed a mean increase in QTc that resolved by 15 or 30 min time point. QT interval prolongation was recorded as an adverse event in two subjects in the mild renal impairment group and four subjects in the moderate renal impairment group. This observed transient increase in

QTc after regadenson may be attributed to increases in heart rate with delay in QT adaptation (hysteresis).

Figure 5. Changes in supine heart rate with regadenoson plasma concentrations




Individual changes in heart rate values plotted vs regadenoson plasma concentrations indicated a greater increase at higher regadenoson concentrations (Figure V).

There were no changes noted in supine diastolic and systolic blood pressure with increase in regadenoson plasma concentrations.

Table VIII: Change from baseline in QT and QTc (Bazette and Fredericia corrected) levels after Regadenoson bolus (±SD)

| Time point | Renal Impairment Group | | | | |
|---|---|---|---|---|---|
| | None (n = 6) | Mild (n = 7) | Moderate (n = 6) | Severe (n = 5) | P-values (F-test, Kruskal-Wallis) |
| *QT Interval (msec)* | | | | | |
| 2 min | –42.7 ± 15.7 | –31.9 ± 17.0 | –25.5 ± 20.8 | –27.8 ± 10.9 | 0.38, 0.32 |
| 15 min | –25.5 ± 9.3 | –15.3 ± 6.8 | –16.0 ± 8.2 | –8.0 ± 9.9 | 0.03, 0.06 |
| 60 min | –5.7 ± 6.0 | –5.4 ± 13.8 | –6.8 ± 16.5 | –1.4 ± 7.3 | 0.89, 0.81 |
| *QTc (Bazett's Correction) Interval (msec)* | | | | | |
| 2 min | 41.6 ± 24.2 | 47.3 ± 28.4 | 51.1 ± 11.4 | 22.7 ± 14.2 | 0.17, 0.09 |
| 15 min | 2.3 ± 7.7 | 9.6 ± 8.1 | 7.5 ± 13.3 | 0.7 ± 6.3 | 0.33, 0.29 |
| 60 min | –2.3 ± 11.7 | 0.1 ± 15.0 | –0.4 ± 17.9 | 1.2 ± 11.7 | 0.98, 0.93 |
| *QTc (Fridericia's Correction) Interval (msec)* | | | | | |
| 2 min | 10.3 ± 19.5 | 18.1 ± 20.2 | 22.6 ± 9.1 | 4.4 ± 8.4 | 0.26, 0.13 |
| 15 min | –7.6 ± 5.9 | 0.8 ± 5.8 | –0.9 ± 8.5 | –2.4 ± 3.3 | 0.13, 0.16 |
| 60 min | –3.5 ± 7.8 | –1.9 ± 12.9 | –2.7 ± 14.1 | 0.1 ± 7.1 | 0.96, 0.92 |

In all treatment groups, the absolute QT interval decreased immediately after regadenoson administration and returned to baseline during next 60 minutes (Table VIII). The effect on QT interval may be confounded by drug-related in heart rate increase, Bazette's and Fridericia's formulae were used to correct QT interval. At 2 min after the regadensoson bolus, all four renal impairment groups showed a mean increase in QTc that resolved by 15 and 60 minute time points. In most subjects the maximum increase in heart rate preceded the maximum reduction in QT interval (hysteresis), which results in an artificial prolongation of QTc interval after initial administration of regadenoson.

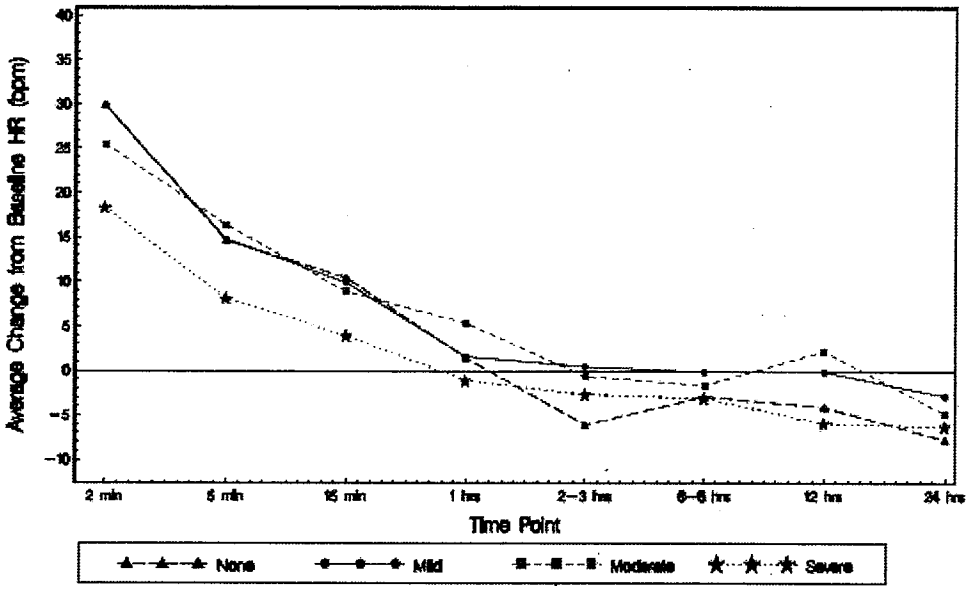
Safety Conclusion:

The type and frequency of adverse events experienced by subjects in this study were similar in the various renal impairment groups. The most frequently reported adverse events included: tachycardia, flushing, headache, dizziness, chest discomfort, QTc interval prolongation, palpitation, and nausea. Adverse events generally started within 5 min after dosing, lasted less than 30 min, and resolved spontaneously. The majority of adverse events were assessed as mild or moderate and probably related to study drug. There were two severe adverse events (flushing and dizziness) in

one subject in the moderate renal impairment group. There were no SAEs and no subjects were prematurely withdrawn due to adverse events.

Administration of regadenoson was associated with a rapid increase (18–30 bpm, depending on treatment group) in heart rate (sinus tachycardia) in all four treatment groups (Figure 6). The mean increase from baseline was greatest at 2 min postdose, returning to within 10 bpm of baseline after approximately 15–60 min. Tachycardia was frequently reported as an adverse event. A small (< 15 mm Hg), transient increase in mean supine systolic blood pressure was observed immediately after regadenoson administration, but there were no clear early effects on systolic standing blood pressure or diastolic blood pressure. At 12 hours postdose, all treatment groups had a transient increase in supine and standing systolic blood pressure, and the moderate and severe groups also had a minor increase in supine and standing diastolic blood pressure. One subject in the moderate renal impairment group experienced mild orthostatic decreases in blood pressure (decrease in systolic blood pressure from supine to standing position of = 20 mm Hg) that were reported as adverse events. This subject also reported moderate dizziness, nausea and headache and mild dry mouth during.

Figure 6. Average change from baseline in heart rate after the start of regadenson injection




STUDY 5123: Effect of Caffeine on Regadenoson Induced MBF

The primary objective of this study was to evaluate the effect of a 200-mg oral dose of caffeine on the regadenoson-induced increase in myocardial blood flow (MBF), measured approximately 2 hours after caffeine ingestion. The secondary objectives were to evaluate regadenoson-induced heart rate (HR) response with and without caffeine and to evaluate the relationship between the regadenoson-induced MBF and HR and BP, and whether they are altered by oral caffeine.

This study was a randomized, double-blind, cross-over study of regadenoson in normal subjects with and without caffeine. Resting and stress PET scans were performed following regadenoson administration (400 microgram IV dose) administered over 10 seconds, following 5 mL of saline flush and following dosing with caffeine 200 mg or placebo on each of the two study days. O-15 water was used as the radionuclide in PET scans. There was 1-14 day washout period between dosing days. Blood samples and measures of safety were collected until 120 minutes after study drug administration.

A total of 52 subjects were enrolled in the study with 26 in each of the cross-over sequence. The primary efficacy measure was the log coronary flow reserve (CFR), which is the ratio of stress MBF after regadenoson dosing to the resting MBF. Plasma caffeine, theophilline, and regadenoson concentrations were measured, and were to be used in exploratory analysis. The primary efficacy analysis was to test whether caffeine reduces CFR after regadenoson administration by at least 10%, using an analysis of variance (ANOVA) with terms of sequence, subject-within-sequence, period and treatment. The limits of the 95% and 90% confidence intervals (CIs) for the difference of treatment means value (caffeine-placebo; log scale) were to be exponentiated to obtain CIs for the ratios of the raw-scale media values. If the lower limit of this latter 90% CI exceeded 0.9, it could be stated with 95% confidence that prior caffeine administration reduces CFR by less than 10%.

Results: The log CFR ± SE for the placebo group (n=40) was 1.03 ± 0.06 and log CFR for the caffeine group (n=40) was 0.95 ± 0.06. The CFR (stress/rest) for the placebo group was 2.97 ± 0.16 and for the caffeine group was 2.75 ± 0.16.

While there was no change in CFR detected in this study, the study does not rule out nor does it establish a significant interaction between regadenoson and caffeine on log CFR. The exponentiated upper and lower limits of the 95 and 90% confidence intervals for log CFR (caffeine versus placebo difference) are 1.08 and 0.78 and 1.06 and 0.80, respectively. Since this lower limit is less than 0.9, but the upper limit is > 1, this study cannot establish or rule out an interaction. However, there is 95% confidence that the change in CFR is not = 20%.

Safety Results:

AEs occurred at any time in the following classes by percentage of subjects: cardiac disorders 25/43 (58%), respiratory, thoracic and mediastinal disorders 25/43 (58%), nervous system disorders 18/43 (42%), vascular disorders 13/43 (30%), musculoskeletal and connective tissue disorders 12/43 (28%), general disorders and administration site conditions 11/43 (26%), gastrointestinal disorders 2/43 (5%), and ear and labyrinth disorders 1/43 (2%).

The most frequently occurring AEs were dyspnoea 24/43 (56%), palpitations 21/43 (49%), flushing 13/43 (30%), headache 12/43 (28%), sensation of heaviness 12/27 (28%), and paraesthesia 8/43 (19%).

Forty percent (17/43) of subjects had at least one AE with a maximum severity of mild, 49% (21/43) moderate, and 9% (4/43) severe. Ninety-five percent of subjects (41/43) had at least one AE that was considered probably related and 2% (1/43) of patients had at least one AE that was considered possibly related to regadenoson treatment. Regadenoson-induced headache severity was decreased with caffeine ($p = 0.012$). There were no reported deaths or SAEs.

Caffeine attenuated the HR increase caused by regadenoson ($p < 0.001$). There was no effect of caffeine on systolic or diastolic blood pressures in the presence of regadenoson.

After regadenoson dosing, one subject appears to have developed first degree AV block, and one subject appears to have had QTc prolongation (> 500 msec and change of > 60 msec) as determined by ECG analysis that were not reported as AEs.

According to the tolerability questionnaire, subjects felt more comfortable during the test with caffeine ($p < 0.001$), and felt better after the caffeine test than after the placebo test

Conclusion:

While there was no change in CFR detected in this study, the study does not rule out nor does it establish a significant interaction between regadenoson and caffeine on log CFR. The exponentiated upper and lower limits of the 95 and 90% confidence intervals for log CFR (caffeine versus placebo difference) are 1.08 and 0.78 and 1.06 and 0.80, respectively. Since this lower limit is less than 0.9, but the upper limit is > 1, this study cannot establish or rule out an interaction. However, there is 95% confidence that the change in CFR is not = 20%.

There was no significant interaction of caffeine with regadenoson on CFR by sex.

There was no difference in overall incidence of AEs between the placebo and caffeine groups; however, caffeine attenuated the severity of AEs. Regadenoson-induced headache severity was decreased with caffeine.

The most frequently occurring AEs were dyspnoea 24/43 (56%), palpitations 21/43 (49%), flushing 13/43 (30%), headache 12/43 (28%), and sensation of heaviness 12/27 (28%), paraesthesia 8/43 (19%).

Caffeine attenuated the HR increase caused by regadenoson ($p < 0.001$). There was no effect of caffeine on systolic or diastolic blood pressures in the presence of regadenoson.

According to the tolerability questionnaire, subjects felt more comfortable during the test with caffeine ($p < 0.001$), and felt better after the caffeine test than after the placebo test

Study 5121:

The primary objective was to identify an optimal dose regimen of regadenoson (CVT-3146) that would cause a = 2.0-fold increase in average peak velocity (APV) above baseline that would last at least 2 minutes in subjects undergoing a clinically indicated cardiac catheterization.

The secondary objectives were to evaluate the dose (concentration)-response relationship for the effect of regadenoson on APV of coronary blood flow (CBF) and the pharmacokinetics of regadenoson in subjects with preserved and reduced left ventricular ejection fraction (LVEF); to assess whether aminophylline acts as an antagonist to the effects of regadenoson; and to assess the safety and tolerability of regadenoson administered as a single intravenous (IV) bolus dose to subjects undergoing a clinically indicated cardiac catheterization.

Methodology: This was a Phase II, open-label, single-dose study in subjects undergoing a clinically indicated cardiac catheterization. Subjects were enrolled into one of three study parts: A, B, or A1. Part A was a dose-escalation study, evaluating up to five dose levels: 30, 100, 300, 600, and 900 µg regadenoson until a dose was identified that increased APV to twice the baseline level for at least 2 minutes and that was well tolerated. Dose escalation was to proceed only if lower doses were tolerated and APV data suggested that escalation was investigationally necessary. Intermediate doses were to be studied to adequately describe the dose-response relationship, as necessary. In Part B, subjects with a reduced LVEF were dosed with a single dose of 30 µg of regadenoson. In Part A1, subjects were given a single dose of 400 µg of regadenoson followed in 1 minute by 100 mg of aminophylline.

On the day of the study, and prior to administration of regadenoson, baseline laboratory tests and a coronary angiography were performed; during the angiography, a study vessel was selected (left anterior descending coronary artery [LAD] or left circumflex coronary artery [LCx]) and study eligibility was confirmed (= 50% stenosis in LAD or LCx, no severe coronary stenosis [= 70% diameter reduction unless vessel had a widely patent graft], no aortic stenosis with valve area < 1.5 cm2, no obstructive cardiomyopathy). The selected study vessel (LAD or LCx) was challenged by up to three intracoronary (IC) injections of 18 µg adenosine. Doppler measurements of APV were recorded prior to adenosine challenge and during maximal hyperemia. If the study vessel responded to adenosine with a ratio of peak to

baseline APV (coronary flow velocity reserve [CFR]) = 2.5, the subject qualified for study inclusion. Prior to administration of regadenoson, another baseline Doppler measurement of APV was recorded. After administration of study drug, APV was continuously monitored and recorded until it returned to baseline or for 30 minutes postdose, whichever occurred first.

Number of subjects enrolled:

Part A of this study enrolled 40 subjects, Part B enrolled 4 subjects, and Part A1 enrolled 4 subjects. In Part A, 34 subjects were dosed. In Part B, 2 subjects were dosed. In Part A1, 4 subjects were dosed. Efficacy data were evaluable in 27 subjects in Part A, 1 subject in Part B, and 4 subjects in Part A1. All dosed subjects completed the study.

Diagnosis and Main Criteria for Inclusion:

Subjects were eligible for study participation based on the following main criteria: male or female adults = 18 years of age, undergoing a clinically indicated cardiac catheterization for evaluation and/or treatment of suspected ischemic heart disease, had = 50% stenosis in the ungrafted study vessel (either LAD or LCx) on the day of the study, had a normal electrocardiogram (ECG) at screening and predose or an abnormal ECG not considered to reflect ongoing or frequently recurrent ischemia, and had a documented study vessel peak to baseline APV ratio = 2.5 after IC administration of 18 μg adenosine on the day of study. In addition, female subjects were to be postmenopausal, surgically sterile, or using an acceptable method of contraception; they must not have been pregnant (as verified by a serum pregnancy test within 24 hours prior to dosing) nor breast-feeding.

Test Product, Dose and Mode of Administration, Batch Number:

Regadenoson for IV administration was supplied as a sterile stock solution in single-use vials. Prior to Amendment 4 of the protocol, each single-use vial contained 10 mL of 0.2 mg/mL regadenoson solution, which was to be diluted with sterile saline prior to administration. Following protocol Amendment 4, each vial contained 5 mL of a 0.1 mg/mL regadenoson solution that was to be diluted with a CVT-supplied diluent prior to administration. Vials of regadenoson stock solution were to be stored in a

secure area under ambient conditions (15–30°C for the 0.1 mg/mL vials and = 30°C for the 0.2 mg/mL vials) and were not to be frozen (0.1 mg/mL vials were also not to be refrigerated). Regadenoson stock solution used in this study had the following lot numbers: 803395 (0.1 mg/mL) with 803392 (diluent) and 4P9002 (0.2 mg/mL).

Planned doses for evaluation were 10, 30, 100, 300, 600, and 900 µg. Actual doses evaluated were 10, 30, 100, 300, 400, and 500 µg of regadenoson. Subjects were to receive a single, 5-mL bolus dose of regadenoson, immediately followed by a 5-mL saline flush.

Adenosine stock solution (3 mg/mL, [redacted]) was to be diluted with saline (1 mL of solution with 250 mL saline). An IV injection (1.5 mL) of the resultant solution (12 µg/mL) was administered. Commercially available aminophylline was used, as appropriate. For Part A1 of the study.

Efficacy: Efficacy was assessed through APV measurements by pulsed-wave Doppler ultrasonography. The primary efficacy variable (Part A) was defined as the time (in seconds) that the ratio of APV to baseline APV following administration of regadenoson was at least 2.0. Other APV measures included: (1) the ratio of peak APV to baseline APV, (2) the time of peak APV, (3) the time of near-peak APV (APV = 85% of peak), (4) the ratio of APV to baseline APV, and (5) the ratio of peak APV to baseline APV, expressed as a percentage of CFR. Data from Parts B and A1 were compared with those of subjects who received the same dose level in Part A. Ratios of peak APV to baseline APV over time and changes from baseline heart rate (HR) were compared between the study parts.

Pharmacokinetics: Both non- compartmental-computed parameters ($t_{1/2}$, Cmax, AUC, CL, and Vss) and compartmental analysis were used to describe the concentration-time data for regadenoson.

Efficacy Results: The evaluated doses of regadenoson that resulted in at least a 2-fold increase in mean APV from baseline for at least 2 minutes were 300, 400, and 500 µg (Table IX). At the 400 µg and 500 µg doses, the effect was more sustained (magnitude and duration of response); peak flow was = 2.5 times baseline for a median duration of 2.79 minutes and 2.85 minutes, respectively. Following administration of aminophylline, the effect of regadenoson on APV was considerably shortened and subjects returned to baseline APV within 2 minutes. There were too few subjects with reduced

LVEF to ascertain whether the effect of regadenoson was different between subjects with reduced versus normal LVEF. Only one subject with reduced LVEF had evaluable data, and in this subject, the time to peak APV and the duration of APV were longer than the corresponding values in subjects receiving the same regadenoson dose and with normal LVEF.

Table IX. Duration of APV at least 2X or 2.5X that of baseline APV following regadenoson administration

| Parameter | Regadenoson Dose Group (mcg) | | | | | |
|---|---|---|---|---|---|---|
| Statistic | 10 | 30 | 100 | 300 | 400 | 500 |
| **Time ≥ 2X Baseline APV (sec)** | | | | | | |
| n | 4 | 4 | 2 | 4 | 8 | 4 |
| Mean (SD) | 19.5 ( 38.91) | 17.6 ( 12.03) | 64.4 ( 46.94) | 323.6 (433.21) | 625.2 (590.53) | 468.8 (393.71) |
| CV (%) | 200 | 68 | 73 | 134 | 94 | 84 |
| Median | 0.0 | 21.5 | 64.4 | 138.5 | 522.4 | 491.0 |
| Min - Max | | | | | | |
| **Time ≥ 2.5X Baseline APV (sec)** | | | | | | |
| n | 4 | 4 | 2 | 4 | 8 | 4 |
| Mean (SD) | 0.6 ( 1.15) | 4.1 ( 5.50) | 12.3 ( 12.82) | 212.1 (324.10) | 326.1 (429.30) | 200.4 (195.54) |
| CV (%) | 200 | 135 | 104 | 153 | 132 | 98 |
| Median | 0.0 | 2.3 | 12.3 | 79.7 | 167.4 | 171.1 |
| Min - Max | | | | | | |

Pharmacokinetic Results:

Regadenoson pharmacokinetics was best described by a 3-compartment model, with the regadenoson plasma concentration-time profile following a tri-exponential decay. The regadenoson plasma concentrations declined with fast distribution phases followed by a relatively longer elimination half-life. Regadenoson plasma concentrations increased to a maximum within 1–3 minutes after drug administration in most subjects. The delay was attributed to opposite arms being used for drug administration and plasma sampling. Body weight was found to correlate with the central volume of distribution of regadenoson and inclusion of body weight in the PK model improved the fit of the model. The effect, however, was rather weak, evident by a parameter estimate of 1.05 for the slope factor. Thus, body weight is not considered a clinically significant covariate. Regadenoson's effect on APV and HR were satisfactorily described by a saturable system linking drug concentrations in a hypothetical effect compartment to the observed effects.

Safety Results: Forty-eight percent of subjects experienced at least one adverse event. In general, adverse events were transient and self-limiting, occurring rapidly after administration of regadenoson and resolving spontaneously within minutes of onset. In general, more adverse events

occurred with higher doses of regadenoson. The most frequently reported adverse events that were considered related to regadenoson included tachycardia, chest pain, and hypotension. The majority of adverse events were mild; only one was moderate and one was severe. There were two SAEs (an MI and wound secretion), both considered probably not related to regadenoson. Clinical laboratory parameters generally remained within normal limits. Vital signs showed increases in HR with increasing dose, reaching a maximum 1–2 minutes after regadenoson administration. Mean HR increases ranged from 4 bpm (10-µg dose) to 20 bpm (400-µg dose). With increased HR, the QT interval decreased in a dose-dependent manner, with the greatest decrease observed at 2 minutes postdose.

**Study 5123: Effect of Caffeine (200 mg, oral dose) on Myocardial Blood Flow**

The primary objective of this study was to evaluate the effect of a 200-mg oral dose of caffeine on the regadenoson-induced increase in myocardial blood flow (MBF), measured approximately 2 hours after caffeine ingestion. The secondary objectives were: a) To evaluate the regadenoson-induced heart rate (HR) response with and without prior caffeine, b) To evaluate the relationship between the regadenoson-induced increase in MBF and HR changes, and whether it is altered by oral caffeine, c) To evaluate the regadenoson-induced blood pressure (BP) response with and without prior caffeine , d) To assess the safety and tolerability of regadenoson with and without prior caffeine, e) To assess whether the effect of prior caffeine on the MBF response to regadenoson differs between male and female volunteers.

This was a randomized, double-blind, crossover study of regadenoson in normal subjects with and without caffeine. Resting and stress positron emission tomography (PET) scans were performed following regadenoson administration (a single 400 µg intravenous (IV) dose, administered over 10 seconds, followed by a 5 mL saline flush) and following dosing with caffeine 200 mg or placebo on each of 2 study days. O-15 water was used as the radionuclide in the PET scans. There was a 1- to 14-day washout period between dosing days. Blood samples and measures of safety were collected until 120 minutes after study drug administration.

The study was designed to enroll 52 subjects (26 in each crossover sequence) in order that 40 subjects complete the study with evaluable data. There were 45 subjects enrolled and randomized and 43 subjects dosed with regadenoson of which 41 subjects completed the study, 40 subjects were evaluable for efficacy, and 2 subjects terminated prematurely.

**Test Product, Dose, Mode of Administration and Batch Number:**

Open-label study drug was supplied as sterile stock solution in single-use vials each containing 5 mL of regadenoson (0.08 mg/mL). Regadenoson, 400 µg, was administered as a rapid bolus, through an iv catheter over approximately 10 seconds, followed immediately by a 5 mL saline flush. Regadenoson (study drug) had the following CVT lot number: 803604.

On each of 2 study days, subjects received a single dose of regadenoson, administered intravenously as a rapid (10-second) bolus of 5 mL, followed by a 5 mL saline flush. There was a 1- to 14-day washout period between doses.

Reference Drug, Mode of Administration and Batch Number:

Caffeine or placebo capsules (200 mg po) was taken 105 minutes prior to administration of regadenoson. The CVT tracking number for the caffeine capsules was 1341 (Leg 3). These capsules contained caffeine tablets from [redacted] with lot number 405542.

PK:
Blood samples for analysis of regadenoson concentrations were to be drawn and samples were to be processed, stored, and shipped to CVT for analysis. All samples were obtained by collecting approximately 6 mL of blood in a properly labeled heparinized vacutainer tube. After gentle inversion to mix, the tube was to be placed on wet ice immediately. Within 3 hours of collection, the sample was to be centrifuged and the plasma transferred to a polypropylene screw-cap tube and immediately stored frozen at -20°C until it was sent to CVT for bioanalysis. Regadenoson concentrations were measured in plasma samples using the analytical method. This method involves solid-phase extraction of regadenoson and the internal standard from human plasma or urine, and analysis of the extract by high-performance liquid chromatography coupled with mass spectrometry (HPLC/MS/MS) using positive-ion spray ionization. The mass spectrometer

is operated in multiple-reaction-monitoring mode. [redacted] is used as the internal standard for quantification. The quantification range of the method for plasma is 0.100–40 ng/mL using a 0.50 mL aliquot of plasma.

Efficacy Results:

The log Coronary Flow Reserve (CFR) CFR ± SE for the placebo group (n=40) was 1.03 ± 0.06 and log CFR for the caffeine group (n=40) was 0.95 ± 0.06. The CFR (stress/rest) for the placebo group was 2.97 ± 0.16 and for the caffeine group was 2.75 ± 0.16. While there was no change in CFR detected in this study, the study does not rule out nor does it establish a significant interaction between regadenoson and caffeine on log CFR. The exponentiated upper and lower limits of the 95 and 90% confidence intervals for log CFR (caffeine versus placebo difference) are 1.08 and 0.78 and 1.06 and 0.80, respectively. Since this lower limit is less than 0.9, but the upper limit is > 1, this study cannot establish or rule out an interaction. However, there is 95% confidence that the change in CFR is not = 20%. • There was no significant interaction of caffeine with regadenoson on CFR by sex.

There was no difference in overall incidence of AEs between the placebo and caffeine groups; however, caffeine attenuated the severity of AEs. Regadenoson-induced headache severity was decreased with caffeine.

The most frequently occurring AEs were dyspnoea 24/43 (56%), palpitations 21/43 (49%), flushing 13/43 (30%), headache 12/43 (28%), and sensation of heaviness 12/27 (28%), paraesthesia 8/43 (19%).

Caffeine attenuated the HR increase caused by regadenoson ($p < 0.001$). There was no effect of caffeine on systolic or diastolic blood pressures in the presence of regadenoson.

According to the tolerability questionnaire, subjects felt more comfortable during the test caffeine ($p < 0.001$), and felt better after the caffeine test than after the placebo test.

**Study 5124:**

**Title: A Randomized, Double-Blind, Placebo-Controlled, Cross-Over Study to Evaluate the Effect of Regadenoson on Pulmonary Function in AMP-Sensitive Subjects with Mild or Moderate Asthma**

The primary objective of this study was to compare broncoconstrictive reactions, defined as a reduction from baseline Forced Expiration Volume in first second after inhalation of air (FEV1) of greater than 15%, within 2 hours after dosing with a 400 μg regadenoson intravenous (iv) bolus to that following a placebo bolus. The secondary objectives were to compare the mean FEV1 over 2 hours following a 400 μg regadenoson iv bolus to that following a placebo bolus; to compare the peak FEV1 change within 2 hours after dosing with regadenoson to that after dosing with placebo; to compare the time of peak FEV1 change and duration of change within 2 hours after dosing with regadenoson to those after dosing with placebo; to investigate the regadenoson-induced heart rate and blood pressure response; and to assess the safety of regadenoson in this population.

This Phase 2 study was designed to determine whether regadenoson would elicit a bronchoconstrictive response in subjects with AMP-sensitive mild or moderate asthma. Patients with reactive airway disease (asthma) who develop bronchoconstriction following AMP challenge could be expected to develop bronchoconstriction after systemic administration of adenosine and are thus an ideal population to test susceptibility to bronchospasm associated with the use of regadenoson. The proposed assessments of airway reactiveness as well as other cardiac and physical symptoms were appropriate to study the safety of regadenoson in this subject population, and determine whether regadenoson has the potential of being associated with bronchospasm in the target population with mild and moderate asthma. The efficacy of regadenoson was not evaluated in this study; the objective was to evaluate safety, focusing on spirometry measures (indicative of bronchoconstriction), in subjects with AMP-sensitive mild to moderate asthma.

**Methodology**: This was a double-blind, Phase 2, cross-over study designed to evaluate whether regadenoson at a dose to be used for myocardial perfusion imaging in the detection of coronary artery disease (i.e., a 400 μg bolus) elicited a bronchoconstrictive response in subjects with AMP-sensitive mild or moderate asthma.

Subjects in this study were selected based on a history of asthma and a measured reduction in FEV1 of at least 20% following a standard adenosine monophosphate (AMP) challenge at screening. Subjects were to receive 400 μg regadenoson or placebo administered as an iv bolus in a double-blind, cross-over design. Repeated measurements of FEV1 as an assessment of bronchoconstriction were to be performed before and for up to 2 hours after study drug administration. Other safety variables were followed over the same period of time. When 24 mild asthma subjects had completed the study, a safety review of the data was to be conducted. If the data demonstrated that regadenoson was safe based on a series of predetermined clinical criteria, recruitment of moderate asthma (n = 24) subjects was to commence. The treatment and assessments were to be the same as for the mild asthma subjects.

**Number of Subjects (Planned and Analyzed)**: Up to 48 evaluable subjects were to be enrolled. There were 24 mild and 24 moderate asthma subjects actually enrolled and analyzed in the study; 47 subjects completed both treatment periods (regadenoson and placebo), and 1 subject withdrew from the study due to an adverse event after completion of only one treatment period (placebo).

**Diagnosis and Main Criteria for Inclusion:** Men or women = 18 years of age with a diagnosis of mild or moderate asthma as documented by clinical history and pulmonary function test were considered for inclusion.

Mild asthma subjects must not have had corticosteroids (inhaled or oral) within 8 weeks prior to the screening visit and must have had an FEV1 = 80% of the predicted value at screening.

Moderate asthma subjects may have been taking corticosteroids and must have had an FEV1 > 60% and < 80% of the predicted value at screening.

In addition, each subject must have: signed an informed consent form, been on a stable bronchodilator regimen for at least 3 weeks prior to screening, and had a pulse oximetry reading of = 92% at baseline. For each subject, administration of inhaled AMP in accord with the site's protocol for AMP challenge testing must have been considered clinically safe; results of the AMP challenge should have demonstrated a PC20 to AMP < 400 mg/mL. Subjects must have abstained from short acting bronchodilator use for at least 6 hours prior to dosing with AMP, regadenoson, or placebo, and for 2 hours after dosing with regadenoson, or placebo, and abstained from theophylline and/or long acting bronchodilators for 24 hours prior to dosing with AMP (moderate asthma subjects only), regadenoson, or placebo.

Subjects must have been able and willing to abstain from any intake of caffeine or other methylxanthines for 24 hours prior to the AMP challenge test and each blinded dosing, abstain from smoking for 24 hours prior to study drug administration, abstain from eating and drinking 30 minutes prior to study drug administration through to the completion of the pulmonary function test, on both dosing days, and comply with the protocol.

Female subjects of child-bearing potential must have used an acceptable method of contraception and must have had a negative pregnancy test at screening and prior to each dosing day or must have been post-menopausal or surgically sterile.

**Efficacy**: Not applicable.

**Safety**: Safety was evaluated through spirometry measurements, adverse events, identification of serious adverse events, concomitant medications, physical examination findings, vital signs, electrocardiogram measurements, and laboratory assessments.

The primary spirometry variable was the incidence of bronchoconstrictive reactions, defined as a reduction from baseline FEV1 of greater than 15% within 2 hours after dosing with an iv bolus of the study medication. Secondary spirometry variables included postdose FEV1 averaged across the 10, 20, 30, 45, 60, 90, and 120 minute time points, FEV1 / baseline FEV1 at each time point, minimum FEV1 / baseline FEV1 (maximum FEV1 reduction) across the time points, and earliest time of minimum FEV1. For each subject, FEV1 and percent change from baseline FEV1 were to be

plotted vs time postdose, with data for both treatment periods shown in the same panel.

Safety Results:

In this study, the overall incidence of bronchoconstriction was 8%; none of the subjects with mild asthma and 4 (17%) subjects with moderate asthma experienced bronchoconstriction, defined as a decrease from baseline FEV1 of > 15%. Bronchoconstriction occurred after placebo dosing for 2 subjects and after regadenoson dosing in 2 other subjects. The greatest decrease in FEV1 (36.2%) was observed in one subject with moderate asthma at the 90-minute time point following regadenoson dosing.

For all subjects in the study, there was no difference in mean postbolus FEV1 between the regadenoson and placebo groups. Similarly, mean FEV1 values for mild and moderate asthma subjects appeared similar when comparing regadenoson and placebo treatments. Mean changes from baseline FEV1 appeared similar between regadenoson and placebo over time.

More AEs were observed in subjects after receiving regadenoson than placebo. After receiving regadenoson, the majority (98%) of subjects had at least one AE; following placebo, 8% of subjects had an AE.

Following regadenoson dosing, 30% of subjects had at least one AE considered mild, 53% moderate, and 15% severe in intensity. The majority of subjects had AEs that were considered probably (96%) or possibly (2%) related to regadenoson. The most common AEs with regadenoson were tachycardia (66%), dizziness (53%), headache (45%), dyspnoea (34%), flushing (32%), chest discomfort (21%), nausea (19%), paraesthesia (19%), and pain in extremity (9%).

Following regadenoson administration, 17 subjects (11 mild and 6 moderate asthmatics) had at least 1 AE involving the pulmonary system; following placebo dosing, 1 subject (with moderate asthma) had a similar AE. One subject with moderate asthma prematurely withdrew after receiving placebo due to worsening asthma.

Conclusion:

In an AMP-sensitive population, there was no significant difference in incidence of bronchoconstriction, defined as a decrease in FEV1 of > 15%, between subjects taking regadenoson vs placebo (2 subjects with regadenoson and 2 others with placebo). No subject with mild asthma had a bronchoconstrictive reaction. Regadenoson was well tolerated in the mild asthma group. In the moderate asthma group, bronchoconstriction occurred in an equal number of subjects receiving regadenoson and placebo (2 following placebo and 2 others following regadenoson, p = 0.99). However, after receiving regadenoson, one subject had a clinically significant decrease in FEV1 of -27% at 45 minutes postdose with a nadir of -36% at 90 minutes postdose.

The AEs observed with regadenoson were consistent with the pharmacologic effects of this drug and included tachycardia, dizziness, headache, dyspnoea, flushing, and chest discomfort. Other frequently reported AEs in this study included nausea, paraesthesia, and pain in extremity. Regadenoson caused a transient and significant increase in HR, and these changes were similar in mild and moderate asthma patients.

STUDY CVT 5125: This was a pilot randomized, double-blind, placebo-controlled, two-period crossover study to evaluate the safety of Regadenoson in Chronic Obstructive Pulmonary Disease (COPD) subjects.

Methodology: Up to 48 subjects with moderate (Stage II) and severe (Stage III) COPD were randomized in a double-blind fashion to a sequence of treatment (regadenoson/placebo or placebo/regadenoson) in a crossover design trial with a crossover period of 7–14 days between the first and second treatments. The trial was conducted in two phases. The first phase enrolled 15 moderate COPD subjects. An independent safety assessment was performed following the enrollment of the first 15 subjects. The independent reviewer had the option to have multiple safety reviews for this study, as was appropriate. Enrollment of severe COPD subjects in the second phase of the study proceeded only after approval of the independent assessor. No more than 38 moderate COPD subjects were allowed to enroll in the study. Subjects who prematurely terminated from the trial were not replaced.

Number of Patients (Planned and Analyzed): Approximately 48 subjects with moderate or severe COPD enrolled, with no more than 38 subjects having moderate COPD. Total enrollment was 49 subjects with 38 moderate COPD subjects and 11 severe COPD subjects enrolled in the study.

Diagnosis and Main Criteria for Inclusion: Subjects were to have had moderate or severe COPD (Stages II and III, respectively) based on spirometric assessment conducted within 6 months of the first day of study treatment. In addition, subjects were to have been able to safely abstain from short-acting bronchodilators for 2 hours after dosing of study drug and for at least 8 hours before study drug treatment, were willing and able to sign an informed consent form and HIPAA authorization and to comply with study procedures, were = 18 years of age, were able to safely abstain from any intake of caffeine or other methylxanthine-containing foods for 24 hours prior to each study drug treatment, and were able to abstain from eating and drinking for 30 minutes and smoking for 3 hours prior to study drug administration and to the end of the last study measurement on each dosing day. Female subjects of childbearing potential were to have had negative urine pregnancy tests at screening and prior to each dosing day.

The following assessments were to be made 30 minutes prior to study drug administration:

• Obtain baseline FEV1 and FVC based on 3 measurements obtained within 30 minutes prior to drug dosing. The set of 3 values each of FEV1 and FVC were required to meet ATS criteria for acceptability and reproducibility. If the values did not meet the criteria, then additional values were to be obtained up to a maximum of 8 values until a set of FEV1 and FVC measurements fulfilled the criteria.

• The baseline FEV1 was defined as the highest acceptable FEV1 obtained prior to dosing.

• The baseline FEV1 prior to each study treatment was to be within 20% of the screening PFT's FEV1. Subjects whose baseline FEV1 deviated from the screening FEV1 by more than 20% were not to receive study drug treatment.

The following procedures were to be performed 15 minutes prior to study drug administration:

• Begin continuous monitoring of oxygen saturation using a pulse oximeter and of heart rhythm using telemetry.

• Record baseline oxygen saturation as follows:

– Two oxygen saturation measurements were to be made 5 minutes apart and within 15 minutes prior to administration of study drug treatment. Oxygen saturation was to be measured every 10 seconds over 1 minute.

• Conduct a pulmonary examination as follows:

– Record wheezing as either being absent or present over each of 6 lung fields. The pulmonary exam was to include determination of the presence of rhonchi, accessory respiratory muscle use, prolonged expiratory phase, distant breath sounds, paradoxical abdominal breathing, and pursed-lip breathing. • Obtain a 12-lead ECG. • Obtain 2 baseline blood pressure (BP), HR, and respiratory rate measurements that were 5 minutes apart and within 15 minutes prior to administration of study drug. • Record concomitant medications and AEs.

Administration of Study Drug:

Over 10 seconds, 5 mL of study drug was to be injected iv, immediately followed by a 5 mL 0.9% sodium chloride injection USP (saline) flush.

A blood sample was to be taken for measurement of regadenoson 1 minute after the study drug bolus and saline flush.

Postdose Procedures:

After study drug administration, the following procedures were to be performed:

• Postdose FEV1 measurements were to be taken at 5, 15, 30, 45, 60, 90, and 120 minutes and at anytime when the subject felt short of breath or wheezing developed.

5 minutes postdose:

• A 12-lead ECG, was to be obtained. • Measure BP, HR, and respiratory rate. • Conduct a pulmonary examination. • Obtain up to 5 FEV1 measurements until two values that meet ATS criteria for acceptability and reproducibility.

15, 30, 60, and 90 minutes postdose:

• Obtain a 12-lead ECG. • Measure BP, HR, and respiratory rate.

• Record oxygen saturation. • Conduct a pulmonary examination. • Obtain up to 5 FEV1 measurements until two values that meet ATS criteria for acceptability and reproducibility.

45 minutes postdose:

• Conduct a pulmonary examination. • Obtain up to 5 FEV1 measurements until two values that meet ATS criteria for acceptability and reproducibility.

120 minutes postdose:

• Obtain a 12-lead ECG. • Measure BP, HR, and respiratory rate. • Record oxygen saturation. • Conduct a pulmonary examination. • Obtain up to 5 FEV1 measurements until two values that meet ATS criteria for acceptability and reproducibility. – If FEV1 was < 85% of baseline at 120 minutes, FEV1 measurements were to continue to be made every 15 minutes until the FEV1 had returned to at least 95% of baseline. If the FEV1 had not returned to within 95% of baseline by the end of 3 hours post-treatment, it was to be periodically followed through the follow-up period of the trial (14 days following the 2nd treatment) until it had stabilized or returned to baseline.

• In these subjects, oxygen saturation, blood pressure, and telemetry monitoring was to continue until return of FEV1 to baseline. Return to baseline was defined as FEV1 at least 95% of baseline FEV1. These subjects may have received a short acting inhaled ß2 agonist, at the discretion of the investigator.

• For subjects whose FEV1 was not back to baseline value at 120 minutes, a final physical examination was to be conducted once the FEV1 returned to baseline.

RESULTS:

Pulmonary Measurements:

FEV1 Measurements:

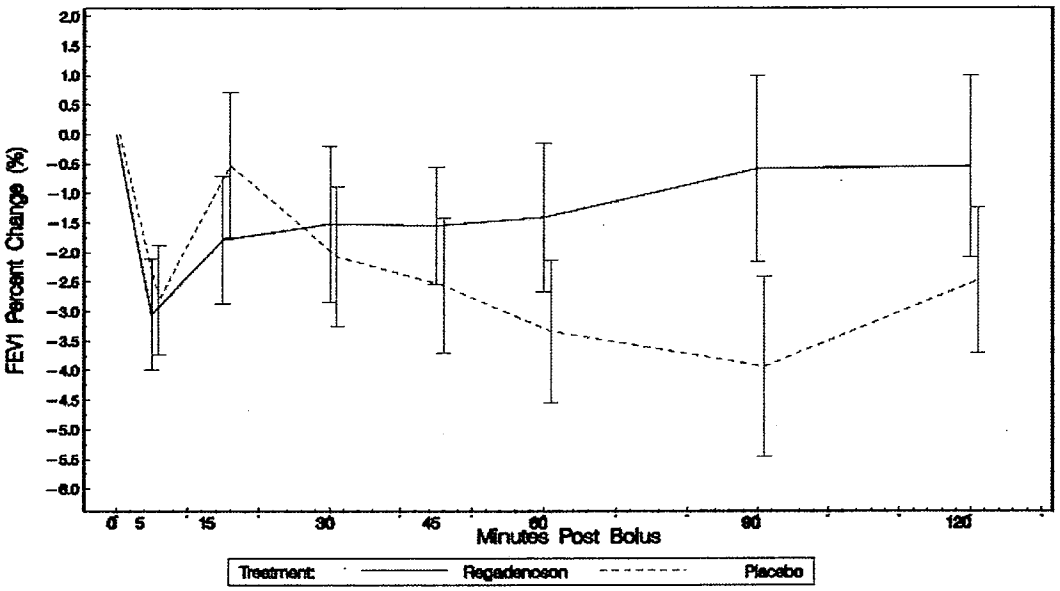
At no point during the 120 minute post-treatment period, for all combined subjects, did the mean change in FEV1 from baseline differ significantly between regadenoson and placebo treatment ($p = 0.2$ for all comparisons). The mean and median changes from baseline in FEV1 were also similar following regadenoson and placebo at each time point. The change in mean percent predicted FEV1 from baseline was also similar following regadenoson and placebo at all timepoints through 120 minutes ($p = 0.21$ for all timepoints). Similar patterns were seen in the subset of subjects with moderate and severe COPD.

The percent change from baseline in FEV1 at each time point through 30 minutes was similar following regadenoson and placebo (Figure 7). However, the curves appear to progressively separate between 30 and 90 minutes postdose, such that the mean percent decline following placebo appeared to be greater than that following regadenoson.

The mean ratio of all post-bolus FEV1/baseline FEV1 time points was also not statistically different between regadenoson and placebo for all time points but 90 minutes postdose (0.98 [0.09] following regadenoson vs 0.97 [0.09] following placebo; $p = 0.04$. The least squares mean ratio of the minimum post-bolus FEV1/baseline FEV1 was 0.92 (0.07) following regadenoson and 0.93 (0.07) following placebo; $p = 0.30$.

These findings together suggest that regadenoson does not cause greater FEV1 decline compared to placebo.

Figure 7. % Change from baseline in FEV1 at each post-bolus time point




Oxygen Saturation:

Oxygen saturation excursions were minimal during the study. No subject developed an oxygen saturation of < 87% at any time point. The maximal decline (LSMean [SE]) in oxygen saturation within 120 minutes of treatment was similar following regadenoson and placebo: 1.20% (0.19%) and 1.11% (0.19%), respectively, p = 0.72. The maximal decline in oxygen saturation was also similar following regadenoson (range: -1.13% to 5.63%) and placebo (range: -2.00% to 5.63%). (Note: Positive numbers indicate a decline from baseline and negative numbers indicate an increase from baseline).

Results:

In this study including predominately elderly and functionally compromised subjects with moderate and severe COPD, there were no deaths, SAEs, AEs resulting in study termination, or treated pulmonary AEs. AE frequency was greater following regadenoson (86%) compared to following placebo (12%); pulmonary AEs, the vast majority of which were dyspnea, occurred only following regadenoson.

The most common AEs following regadenoson were: dyspnea (61.2%), headache (34.7%), flushing (38.8%), dizziness (26.5%), nausea (14.3%), and chest discomfort (12.2%). Self-limited dyspnea of short duration occurred commonly following regadenoson treatment; however, the dyspnea did not appear to be correlated with changes in vital signs, oxygen saturation, pulmonary physical examination, or FEV1.

Through the 120 minute assessment period, there was no statistically significant difference in FEV1 at any time point following regadenoson versus placebo and the nadir FEV1 was similar following both treatments.

Table IX. Incidence of broncoconstriction (>15% decline in FEV1)

| **All Subjects (n = 49)** | | | | | |
|---|---|---|---|---|---|
| | | **Bronchoconstriction on Placebo** | | | **95% CI for difference in proportions p-value[a]** |
| | | Yes | No | Total | -6%–18% 0.31 |
| **Bronchoconstriction on Regadenoson** | Yes | 0 | 6 | 6 (12%) | |
| | No | 3 | 40 | 43 | |
| | Total | 3 (6%) | 46 | 49 | |
| **Subjects with Moderate COPD** | | | | | |
| | | **Bronchoconstriction on Placebo** | | | **p-value[b]** |
| | | Yes | No | Total | 0.13 |
| **Bronchoconstriction on Regadenoson** | Yes | 0 | 6 | 6 (16%) | |
| | No | 1 | 31 | 32 | |
| | Total | 1 (2%) | 37 | 38 | |
| **Subjects with Severe COPD** | | | | | |
| | | **Bronchoconstriction on Placebo** | | | **95% CI p-value[c]** |
| | | Yes | No | Total | NA |
| **Bronchoconstriction on Regadenoson** | Yes | 0 | 0 | 0 | |
| | No | 2 | 9 | 11 | |
| | Total | 2 (18%) | 9 | 11 | |

Nadir oxygen saturation was similar following regadenoson versus placebo.

There was no evidence of an increase in the incidence of new onset wheezing following regadenoson versus placebo. No subject required acute treatment with oxygen or bronchodilators. Bronchoconstrictive reactions, defined as a > 15% decrease from baseline in FEV1 within 120 minutes following treatment occurred both following regadenoson (6/49) and placebo (3/49), p = 0.31. Of these subjects, 3 (2 after placebo and 1 after regadenoson) had a nadir FEV1 > 20% and 1 subject (after placebo) had a nadir FEV1 > 30%. Bronchoconstrictive reactions appeared to be largely clinically silent as there appeared to be no temporally associated pulmonary AEs (other than throat tightness in one subject following regadenoson), vital signs changes, changes in pulmonary examination, or changes in oxygen saturation.

Regadenoson use was associated with a temporary HR increase, and a transient decline in RR and QT interval. There was an apparent prolongation of the QTc interval (Fridericia) possibly due to QT hysteresis.

**4.3 Consult Reviews (including Pharmacometric Reviews):**

**N/A**

## 4.4 Cover Sheet and OCP Filing/Review Form:

**Office of Clinical Pharmacology and Biopharmaceutics**

*New Drug Application Filing and Review Form*

*General Information About the Submission*

| | Information | | Information |
|---|---|---|---|
| NDA Number | 22161 | Brand Name | Regadenoson |
| OCPB Division (I, II, III, IV, V) | V | Generic Name | |
| Medical Division | Division of medical Imaging and Hematology | Drug Class | |
| OCPB Reviewer | Christy S. John, Ph.D. | Indication(s) | stress agent for myocardial perfusion imaging |
| OCPB Team Leader | Young Moon Choi, Ph.D. | Dosage Form | IV bolus (400 microgram) |
| | | Dosing Regimen | 0.08 mg/mL , Total 5 mL |
| Date of Submission | May 14, 2007 | Route of Administration | IV bolus |
| Estimated Due Date of OCPB Review | | Sponsor | CV Therapeutics, Inc. |
| PDUFA Due Date | April 12, 2008 | Priority Classification | |
| Division Due Date | February 12, 2008 | | |

***Clin. Pharm. and Biopharm. Information***

| | "X" if included at filing | Number of studies submitted | Number of studies reviewed | Critical Comments If any |
|---|---|---|---|---|
| STUDY TYPE | | | | |
| Table of Contents present and sufficient to locate reports, tables, data, etc. | X | [redacted] | [redacted] | |
| Tabular Listing of All Human Studies | X | [redacted] | [redacted] | |
| HPK Summary | X | | | |
| Labeling | X | | | |
| Reference Bioanalytical and Analytical Methods | | | | |
| I. Clinical Pharmacology | [redacted] | | | |
| Mass balance: | N/A | | | |
| Isozyme characterization: | X | | | |
| Blood/plasma ratio: | X | | | |
| Plasma protein binding: | X | | | |
| Pharmacokinetics (e.g., Phase I) - | | | | |
| *Healthy Volunteers-* | | | | |
| single dose: | X | | | |
| multiple dose: | X | | | |
| Patients- | | | | |
| single dose: | X | | | |
| multiple dose: | X | | | |
| Dose proportionality - | | | | |

| | | | | |
|---|---|---|---|---|
| fasting / non-fasting single dose: | | | | |
| fasting / non-fasting multiple dose: | | | | |
| **Drug-drug interaction studies -** | | | | |
| In-vivo effects on primary drug: | X | | | |
| In-vivo effects of primary drug: | X | | | |
| In-vitro: | | | | |
| **Subpopulation studies -** | | | | |
| ethnicity: | | | | |
| gender: | | | | |
| pediatrics: | | | | |
| geriatrics: | | | | |
| renal impairment: | X | | | |
| hepatic impairment: | | | | |
| **PD:** | | | | |
| Phase 2: | | | | |
| Phase 3: | | | | |
| **PK/PD:** | | | | |
| Phase 1 and/or 2, proof of concept: | X | | | |
| Phase 3 clinical trial: | X | | | |
| **Population Analyses -** | | | | |
| Data rich: | | | | |
| Data sparse: | | | | |
| **II. Biopharmaceutics** | | | | |
| **Absolute bioavailability:** | **N/A** | | | |
| **Relative bioavailability -** | [redacted] | | | |
| solution as reference: | | | | |
| alternate formulation as reference: | | | | |
| **Bioequivalence studies -** | [redacted] | | | |
| traditional design; single / multi dose: | | | | |
| replicate design; single / multi dose: | | | | |
| **Food-drug interaction studies:** | **N/A** | | | |
| **Dissolution:** | | | | |
| **(IVIVC):** | | | | |
| **Bio-wavier request based on BCS** | | | | |
| **BCS class** | | | | |
| **III. Other CPB Studies** | | | | |
| **Genotype/phenotype studies:** | | | | |
| **Chronopharmacokinetics** | | | | |
| **Pediatric development plan** | | | | |
| **Literature References** | | | | |
| **Total Number of Studies** | | | | |
| | | | | |
| **Filability and QBR comments** | | | | |

| | "X" if yes | Comments |
|---|---|---|
| **Application filable ?** | X | There are a total of eight PK studies conducted by the sponsor in support of this application. The application is filable |
| **Comments sent to firm ?** | | No comments at this point. |
| **QBR questions (key issues to be considered)** | | |
| **Other comments or information not included above** | | |
| **Primary reviewer Signature and Date** | **Christy S. John, August 13, 2007** | |
| **Secondary reviewer Signature and Date** | **Young Moon Choi, August 14, 2007** | |

**CC: NDA XX-XXX, HFD-850(Electronic Entry or Lee), HFD-XXX(CSO), HFD-8XX(TL, DD, DDD), CDR (B. Murphy)**

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/
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Christy John
3/10/2008 01:18:54 PM
BIOPHARMACEUTICS

Young-Moon Choi
3/10/2008 01:26:31 PM
BIOPHARMACEUTICS