CENTER FOR DRUG EVALUATION AND RESEARCH

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MEDICAL REVIEW(S)

CLINICAL REVIEW

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Reviewer Name	Ira Krefting, M.D.
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Established Name	Regadenoson
(Proposed) Trade Name	Lexiscan
Therapeutic Class	IS
Applicant	CV Therapeutics, Inc
Priority Designation	Standard
Formulation	for intravenous use
Dosing Regimen	400 mcg by bolus injection
Indication	Pharmacologic stress agent for myocardial perfusion imaging
Intended Population	Patients with known or suspected coronary artery disease

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1 EXECUTIVE SUMMARY

Nuclear cardiac stress with the associated use of a pharmacologic stress agent (psa) is performed to aid in the diagnosis of coronary artery disease. The role of the pharmacologic stress agent is to produce vasodilatation of the coronary vasculature and subsequently increased coronary artery blood flow. The injected radioactive tracer agent (Thallium, sestamibi, etc) outlines the coronary circulation and has diminished entrance into coronary vessels obstructed by the plaques indicative of coronary artery disease.

The sponsor has presented data to support the contention that Lexiscan is both safe and efficacious to be used as a pharmacologic stress agent in conjunction with nuclear cardiac scanning. Lexiscan performs similarly to existing agents in producing increased coronary artery flow and allowing the identification of ischemic regions of the coronary vascular tree by the nuclear scanning agent. Two identically designed Phase 3 clinical trials with a non-inferiority endpoint served to demonstrate that use of Lexiscan with nuclear stress testing leads to results similar to those obtained with the use of adenosine, a licensed comparator. Based on the initial scans with adenosine, patients were divided into ischemia classes depending on the number of cardiac segments showing reversible ischemia (0-1, small; 2-4, medium; ≥5, large). These classes have clinical correlates; a patient in the small group might be treated expectantly with medications while a patient in the large group could be a bypass candidate. The sponsor shows that the mean difference in results between two separate adenosine stress nuclear scans across a range of ischemia classes is similar to the mean difference between an adenosine and Lexiscan stress nuclear scan across the same range of ischemia classes.

Patients with a clinical indication for a nuclear cardiac stress test without a history of chronic obstructive pulmonary disease, asthma, or second or higher degree heart blocks (without a pacemaker) were candidates to participate. All patients received a baseline nuclear scan without pharmacologic stress; then a scan utilizing adenosine as the pharmacologic stress agent, and then at a later date received another nuclear cardiac stress test with a double-blind randomized stress agent (either adenosine or Lexiscan). The sponsor did enrich the Phase 3 studies by limiting the number of patient participants with normal scans; these patients had an adenosine scan but did not go on to have a randomized scan. The initial rest and adenosine scans were read at the testing site to make clinical decisions; then the patient had a repeat stress test with the randomized agent; and then all the scans were independently read by 3 outside experts. The readings by this group of experts were used for the primary efficacy assessments of the Phase 3 studies. Lexiscan met the non-inferiority criterion established by the sponsor. Hence in terms of defining ischemia with a pharmacologic stress agent associated nuclear scan, both the use of adenosine or Lexiscan lead to similar findings.

The ultimate gold standard for the diagnosis of coronary artery disease is coronary arteriography, obviously an invasive procedure with procedural complications. The performance of Lexiscan as a psa for the diagnosis of CAD relative to coronary arteriography was assessed. This assessment was done in a relatively small group of approximately 400 patients that went on to coronary arteriography at varying time intervals after the nuclear cardiac scans. This performance was consistent with performance of other stress agents.

The safety findings for Lexiscan are consistent with the pre-clinical data that demonstrate the agent does not greatly effect conduction at the Atrio-Ventricular (AV) node. With the use of Lexiscan there was less of an incidence of second degree heart block compared to adenosine. The main Adverse Event (AE) with Lexiscan was headache. Other AES such as chest pain, dyspnea and angina occurred at approximately the same rate for either stress agent. At the investigators discretion, patients with severe symptoms could have reversal of their symptomatology with an aminophylline infusion.

Based on the efficacy data demonstrating a similar performance to adenosine and the acceptable safety data, This reviewer recommends Lexiscan for approval. This new agent has been demonstrated to work as well as adenosine in defining ischemia in patients undergoing a cardiac nuclear stress test. The risk of precipitation of second degree heart block appears to be lower with Lexiscan compared to adenosine. Headache is more frequent event with Lexiscan than with adenosine. The patient receiving Lexiscan still faces various other AEs with likelihood similar to adenosine; these include chest pain, flushing and dyspnea. There are limited safety data in patients with bronchospastic lung disease.
Following approval the sponsor should commit to a Phase 4 study of Lexiscan in a larger number of patients with bronchospastic lung disease.

1.1 Recommendation on Regulatory Action

As noted above, this reviewer recommends Lexiscan for approval. The evidence that will be put forth in this document demonstrates that Lexiscan is safe and effective based on the results of two independent Phase 3 clinical trails. The sponsor demonstrated that Lexiscan can function as a pharmacologic cardiac stress agent to be used in conjunction with nuclear cardiac scanning. The demonstration of safety and efficacy was evident from the results of two clinical, non-inferiority trials where adenosine, an approved pharmacologic stress agent, was the comparator. Concerns have been raised about the use of Lexiscan in patients with chronic obstructive pulmonary disease (COPD) because Lexiscan has only been formally tested in about 50 patients with this condition. For patients with renal insufficiency the decreased elimination rate of Lexiscan leads to an increased Area Under the Curve (AUC) and the possibility of prolonged tachycardia.
Based on all the data contained in this document, the recommendation for Lexiscan is approval.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

As noted above there are concerns in the area of COPD. In the Phase 2 invasive study of hemodynamic function only 1 patient with diminished left ventricular function received Lexiscan and had a complete set of measurements.

1.2.2 Required Phase 4 Commitments

The recommended Phase 4 clinical study commitments are:

1. A safety study of COPD patients monitoring episodes of bronchospasm or COPD exacerbation following Lexiscan use.
2. A safety study of patients with kidney insufficiency.

1.2.3 Other Phase 4 Requests

None

1.3 Summary of Clinical Findings

CV Therapeutics, the sponsor, proposes Lexiscan (Lexiscan) as a new pharmacologic stress agent (psa) to be used in conjunction with nuclear cardiac scans for the diagnosis of coronary artery disease. The function of Lexiscan is to increase myocardial blood flow through the selective stimulation of adenosine beta receptors (A2a) to produce coronary vasodilatation. This pharmacologically induced increased blood flow acts as a surrogate for exercise in patients with the suspicion of coronary artery who are unwilling or incapable of performing exercise which would in of itself provoke increased coronary artery blood flow. Nuclear cardiac scanning is performed through the injection of a Thallium or similar radionuclide which generally outlines the regions of the coronary circulation; first as a baseline with no stress agent and repeating the scanning with another dose of the radionuclide after injection of a psa. With increased blood flow provoked by the pharmacologic stress agent areas of coronary obstruction not evident on the baseline study are outlined on the second nuclear scan that is obtained following the injection. Regions of the coronary circulation that have no blood flow both at rest and after injection of the myocardial perfusion agent are deemed to be scarred with no possibility of blood flow, even with provocation from the psa. Regions of the coronary circulation that show obstructive blood flow only after the psa are indicative of ischemia where the provocation of increased blood flow has outlined areas of coronary obstruction. The sponsor has used the well accepted cardiac nuclear scanning 17 segment schematic of the heart and the grading of ischemia based on the number of reversible defects found on the blinded cardiac image analysis. The sponsor also employs the Summed Stress Score which is a total of all of the segments showing reversible ischemia.

The existing agents, adenosine and dipyridamole, for use in myocardial perfusion imaging are administered as iv infusions and are associated with important adverse reactions. Problems with adenosine include the development of heart block or bronchospasm in a small percent of patients. Because a number of the adverse reactions caused by adenosine and dipyridamole appear to be mediated by receptor subtypes other than the A2a-AdoR (Adenosine Receptor), a selective agonist of the A2a receptor has the potential to be associated with fewer undesirable effects. Hence the sponsor embarked on the clinical development of Lexiscan, an agent developed to be a more selective agonist of the A2a receptor.

There can be variability in scanning results in the same patient when adenosine provoked scans are done repetitively. Therefore the sponsors have designed their overall study to demonstrate

that the variability between two adenosine scans is similar to the difference between an adenosine and Lexiscan scan.

1.3.1 Brief Overview of Clinical Program

Lexiscan, a selective A2a-AdoR agonist, is proposed as a myocardial perfusion agent to produce coronary vasodilatation and is to be used in conjunction with nuclear cardiac scanning. There have been a total of ten clinical trials in the Phase 1 to Phase 3 development. In the Phase 3 program there have been two identical trials. A total of 1651 subjects/patients have received Lexiscan; in the Phase 3 trials 1339 patients received Lexiscan. In the integrated safety database there are 1563 subjects/patients (Patients from study CVT 5125, a study of Lexiscan in COPD, and from CVT 5126, a study of Lexiscan in exercise, were excluded from this database). All of the subjects/patients in the integrated safety database received one dose of Lexiscan. These subjects/patients received 400 micrograms of Lexiscan, except for 40 in a dosing trial who were given a dose of 500 micrograms. Since this is a new molecular entity not marketed elsewhere in the world there are no post marketing data available.

1.3.2 Efficacy

The sponsor utilized two Phase 3, randomized, double-blind, double-dummy multicenter trials to demonstrate the non-inferiority of Lexiscan when compared to adenosine as a psa. The study population was males and females greater than 18 years old with a clinical indication (such as chest pain) for a pharmacological stress SPECT myocardial perfusion imaging (mpi) study.
The initial gated SPECT MPI stress study was required to have used a 6-minute adenosine protocol without exercise. The Phase 3 protocol used one of three imaging protocols: one-day 99mtechnetium, two-day 99mtechnetium, or one-day dual isotope. If both the rest and the stress images from the initial scan were of good quality and the patient met qualifying criteria (number of ischemic areas), the patient was randomized to have a gated SPECT stress study with either Lexiscan or adenosine (6 minute protocol without exercise) as the pharmacologic stress agent. To facilitate blinding, each patient was to have 2 IV lines, one for a 6-minute infusion of either adenosine or matching placebo and a second IV for a bolus of either Lexiscan or matching placebo. Each patient received both an infusion and a bolus, one of which was active and the other placebo. (Figure 1) The efficacy of Lexiscan was assessed through standardized collection of SPECT images and blinded evaluation of those images at [redacted] by 3 independent readers. Images were evaluated with respect to segmental analysis (17-segment model), image quality, patient diagnosis, presence or absence of ischemia in 4 vascular territories, lung uptake, transient dilatation of the left ventricle, sub-diaphragmatic activity interference, and wall motion.
Pharmacokinetics of Lexiscan were evaluated through collection of blood samples at pre-defined times post dosing, followed by determining of Lexiscan plasma concentrations and estimation of pharmacokinetic parameters using a population-based model.
The safety of Lexiscan was assessed through adverse events, identification of serious adverse events (SAE), clinical laboratory analyses (hematology, serum chemistry, and coagulation), vital signs, physical examinations, and ECGs. (Table 1)

The primary efficacy endpoint was to demonstrate that the strength of agreement between Lexiscan and adenosine images was not inferior to the strength of agreement between two sequential adenosine images. The primary measure of agreement was based on the number of segments with reversible defects (0-1, 2-4, ≥5) on images assessed by three independent expert readers blinded to treatment assignment.
The secondary endpoints were:

- Compare the safety and tolerability of Lexiscan to that of adenosine
- Compare agreement of image pairs (Lexiscan vs. adenosine and adenosine vs. adenosine) with regard to reader Summed Stress Score (SSS), overall findings (normal, abnormal) and a paired side-by-side comparison of ischemic extent determined by the assessment of three independent expert readers blinded to treatment assignment.
- Compare the strength of agreement of Lexiscan and adenosine images to the strength of agreement of sequential adenosine images within subgroups of patients determined by the estimated probability of having coronary artery disease (CAD) based on the Diamond and Forrester classifications.
- For the subgroup of patients for whom angiography results were obtained, compare adenosine and Lexiscan sensitivity and specificity.

The sponsor presents a clinically relevant primary end point given the variability that can occur with repetitive nuclear cardiac testing. The sponsor's approach is to measure reversibility on a per segment level. Segments were counted as having reversible defects if the stress score was greater than the rest score and the rest score was at least 2. The median count across 3 readers was used as the primary analysis variable, grouped as follows:
0-1 (no ischemia)
2-4 (small to moderate ischemia)
≥5 (large ischemia)
The secondary endpoints are also clinically relevant. The use of SSS as a secondary endpoint is appropriate because classically the SDS (Summed Difference Score = Summed Stress Score-SRS Summed Rest Score) is calculated. The statistical analysis is appropriate for the comparison chosen by the sponsor and will be discussed by the statistical reviewer.
The choice of the 400 microgram dose was driven by three factors: In Phase 2 studies (CVT 5121) the sponsor looked for a dose that increased average Peak velocity (APV) by a factor of two, lead to the nuclear imaging studies that appeared similar to adenosine, and had a favorable safety profile.
Study CVT 5121, a Phase 2, was a dose-escalation (10-500 microgram) study to establish the dose of Lexiscan that caused at least a 2-fold increase (above baseline) in coronary blood flow velocity (measured by Doppler) in patients undergoing clinically indicated coronary catheterization. Thirty-six patients have been enrolled in the study and adequate Doppler tracings were obtained in 26 patients. At the 400 and 500 microgram dose levels, APV was sustained at ≥2.5 times baseline for at least 2 minutes. This study was limited because only one subject with reduced Left Ventricular Ejection Fraction (LVEF) was evaluable for efficacy; Whether the effect of Lexiscan on APV differs for patients with reduced and with normal LVEF is unclear.

Additionally, an imaging study (CVT 5122) was performed to confirm that the doses of 400 and 500 micrograms selected from CVT 5121 would produce images similar to those produced with the licensed comparator, adenosine. This Phase 2 multi center study involved 36 patients, 35 were evaluable; 18 receiving 400 micrograms of Lexiscan and the other 18 receiving 500 micrograms. All of the patients, men and women, had already shown a reversible ischemic defect using the established adenosine protocol. Additionally cardiac angiographic finding were available from 2 patients. A consensus review of 3 radiologists showed SPECT agreement between the combined doses of Lexiscan and adenosine. The overall agreement between adenosine and Lexiscan with respect to specific diagnostic category (classification of normal, predominately reversible defects, or predominately fixed defects) was 74% (26/35). The agreement between adenosine and the 400 microgram Lexiscan group was 67% (12/18) and that for the 500 microgram group was 82% (14/17). Overall consensus agreement rates were 86% for the right coronary artery (RCA) territory, 80% for the left anterior descending (LAD) territory, and 77% for the left circumflex (LCx) territory. At each dose, the determination of the extent of ischemic defects with Lexiscan scans appeared to be similar to the extent determined by adenosine scans; the two Lexiscan doses together also appeared to be similar with respect to the likelihood of a comparable extent of ischemic defect rating. In the 2 patients who underwent coronary angiography, not all of the SPECT readers identified the obstructed coronary vessels found at angiography.

Seventy-two percent of patients experienced at least one adverse event, and fewer patients in the 400 microgram group reported adverse events compared to the 500 microgram group (61% vs. 83%). The most commonly reported adverse events included: chest pain (33%), vasodilatation (31%), dyspnea (31%), headache (25%) and dizziness (19%). The frequency of chest pain and headache were similar between the 400 microgram and 500 microgram dose groups. A higher proportion of patients in the 500 microgram dose group reported vasodilatation, dyspnea, and dizziness. The hemodynamic effects showed a median decrease in SBP of -4.3 and -10 mmHg for the 400 and 500 microgram dose groups respectively and two patients in the 500 microgram group had hypotension reported as an adverse event. Hence, with similar activity and increased AE rate in the 500 microgram dose, the dose of 400 micrograms was chosen for the Phase 3 trials.

The adequacy of the dosing studies is limited by trials being performed in relatively few numbers of patients; trial centers tending to use either the 400 or 500 μgram dose and lack of testing of the dose in a significant number of patients with decreased LVEF.

The Phase 2 studies do suggest that Lexiscan could perform with equal efficacy compared to adenosine. Lexiscan also has the advantages of being administered as an IV push as opposed to the IV drip required by adenosine, no instances of high degree Atrio-ventricular block (AV) were noted and there were minimal pulmonary effects such as bronchospasm.

Reviewer's Efficacy Conclusions: Lexiscan performs with similar efficacy when compared to adenosine

1.3.3 Safety

Safety data are available from all 1,651 subjects dosed with Lexiscan and the sponsor also presents a comparative summary of safety data from Lexiscan and adenosine in the two Phase 3 studies (CVT 5131 and CVT 5132). In the Phase 3 program, Lexiscan was studied in the intended patient population: patients with known or suspected CAD who require MPI to stratify risk and guide management. Many of the patients studied had a history of significant co-morbidities (unstable angina or MI, CABG or PTCA, CHF arrhythmias, and diabetes), as might be expected for a patient population with known or suspected CAD.

Safety data for patients who received at least one dose of Lexiscan are included for all of the ten clinical trials. The safety data for CVT 5125 (COPD trial; n=49) and CVT 5126 (low level exercise trial; n=39) were not available in time for integration with the other studies and each of these trials is summarized individually. The safety analysis groups were (Figure 2):

- Set 1: All patients dosed with Lexiscan from Phase 1, 2, 3 trials (n=1,563)
- Set 2: All patients dosed with blinded Lexiscan or blinded adenosine in Phase 3 trials (n=2,015)
- Set 3: All patients dosed with open-label adenosine in Phase 3 trials – included in the number of patients who received randomized study drug are 3 patients (2 Lexiscan and 1 adenosine patient) prematurely terminated from the study due to infusion pump difficulties/errors and for whom no safety data were obtained (n=3469)

Set 1 and Set 2 analyses are used to describe demographics, AEs, other significant AEs, early study termination, intervention, severe AEs, and AEs within each System Organ Class (SOC). The Set 2 analysis compares Lexiscan with adenosine for the intended study population and used for describing the subgroups.

In Set 1, ninety-eight percent of the subjects in 8 studies completed the protocol. Two subjects terminated due to an AE (injection site iv infiltration) and 25 subjects left for non medical reasons. In Set 2 and Set 3 the most common reason for discontinuation prior to randomization (n=1,208; 35%) was failure to meet additional qualifying criteria, primarily the determination that the patient had 0-1 segments with reversible defects after the trial had been closed to such patients. The second most common reason was elective withdrawal (n=149; 4%) with some patients stating they did want to continue or did not want a second stress test.

Overall, the AE profile of Lexiscan was similar to that of adenosine, the pharmacologic stress agent used as comparator in the two Phase 3 studies. Patients in the Lexiscan group had a lower incidence of some AEs (flushing, chest pain, chest discomfit, and angina), but a higher incidence of headache. The incidence of dyspnea was similar in the two treatment groups. The duration of these AEs, although in general short (most resolved with 16 minutes after dosing), was slightly longer after Lexiscan. Although some differences in the pattern of AEs in different subgroups were noted (by gender, body weight, or ischemia size category) none were clinically important. Lexiscan did not show a safety signal in patients with renal insufficiency, patients with COPD, and patients with asthma.

Only one serious (S) AE was attributed to Lexiscan: the exacerbation of an ongoing migraine headache in a patient whose migraine worsened after receiving Lexiscan. AEs considered related to study drug were generally graded as mild and minimal or no treatment was required. No serious consequences of pharmacologic changes induced by Lexiscan (e.g., increase in heart rate (HR) and myocardial perfusion) that allow it to act as a stress agent were seen. Patients

receiving Lexiscan had higher HRs that persisted for slightly longer than in adenosine patients. No patient terminated the study prematurely because of an AE related to Lexiscan, but a few patients (≤1%) terminated prematurely because of AEs. Two Lexiscan patients died: one from complications following abdominal surgery for metastatic carcinoid tumors, and one from a catheterization procedure not specified in the protocol. Neither of these deaths was attributed to Lexiscan.

Although patients with known or suspected bronchoconstrictive or bronchospastic lung disease (e.g., asthma, wheezing noted on physical exam, or history of wheezing requiring a bronchodilator or corticosteroids) were excluded from participation in Phase 3 trials, targeted pilot crossover trials showed no apparent difference in the incidence of a bronchoconstrictive response (defined as a reduction in FEV1 of >15% from baseline) after Lexiscan (2/47 patients) compared to placebo (2/48 patients) in patients with mild or moderate AMP-sensitive asthma (studied in trial CVT 5124), and a numerically increased incidence of bronchoconstrictive response, 12% (6/49 patients) after Lexiscan and 6% (3/49 patients) after placebo, in patients with moderate to severe COPD (studied in trial 5125). None of these bronchoconstrictive responses required treatment. AEs from these studies in patients with asthma or COPD were similar in nature to those seen in the two Phase 3 trials and there was no increase in respiratory symptoms temporally associated with the reduction in FEV1 other than throat tightness in one patient.

Aminophylline was used to reverse the adverse effects of Lexiscan when deemed appropriate by the investigator; 3% of Lexiscan patients and 2% of adenosine patients received aminophylline in the Phase 3 studies. The AEs for which aminophylline was given in Lexiscan patients (angina, headache, ECG ST segment depression, and chest pain) resolved without further treatment.

No clinically significant changes in clinical laboratory values occurred following Lexiscan dosing. ECG findings suggestive of myocardial ischemia, relative ischemia being an intended consequence of the pharmacologic stress, were seen. In the Phase 3 trials, an apparent prolongation of the QTcF interval coincided with the timing of the maximum increase in HR. Since Lexiscan has no direct effect on left ventricular repolarization, but increases HR through sympathetic stimulation, the QTcF increase is attributed to QT hysteresis: QT shortening lags behind the rapid HR increase. ECGs showed a lower incidence of treatment-emergent first degree and second degree AV block in patients who received Lexiscan than in those receiving randomized adenosine, and none of the patients developed third degree AV block.

Pharmacologic stress MPI using Lexiscan as the pharmacologic stress agent resulted in no unexpected safety signals compared to adenosine. The adverse reactions induced by Lexiscan were generally similar in numbers and type to the reactions induced by adenosine. Lexiscan had a numerically lower incidence of flushing, chest pain, chest discomfort, angina, and a numerically higher incidence of headache.

The extent of safety data experience is limited by the exclusion criteria of the Phase 3 trials. Because of the labeling restrictions for adenosine, no patient with significant lung disease was included and hence extensive data of Lexiscan pulmonary effects are unknown. Whereas in practice, clinicians might consider the use of Lexiscan with its theoretical lesser potential for adverse pulmonary effects as an alternative to adenosine for mpi in patients with known pulmonary disease only minimal objective data from Phase 2 trials are available. Due to a quota

on the number of patients with minimal to no reversible defects, the effects of Lexiscan on a large group of normal patients is not known.
During the review process, concerns were raised about the possibility of an increased rate of AEs occurring in patients with lower than average body weights. This concern was based on the sponsor's recommendation that the dose of 400 μg was appropriate for all weight groups. Further analysis of data on weight groups and AE occurrence was requested and received by the FDA. These analyses showed no correlation between AEs and body weight (see Appendix 2, and FDA's statistical review).
Reviewer's Conclusion – Lexiscan induces a number of AEs similar to that of adenosine except for the exacerbation of migraine headaches. Lexiscan had a decreased incidence of the development of high degree AV block and though only a small group was studied, it appears to have lesser pulmonary effects than adenosine.
Lexiscan has a role in the diagnostic armamentarium of pharmacologic stress nuclear cardiac imaging.

1.3.4 Dosing Regimen and Administration

Phase 1 trial CVT 5111 was a double blind, randomized, placebo-controlled, crossover, ascending single iv bolus study involving 36 subjects. The trial revealed that the maximum tolerated dose (MTD) of Lexiscan is 10 microgram/kg in the standing position and 20 microgram/kg in the supine position. Dose limiting events were consistent with a selective adenosine A2a agonist including vasodilatation, dizziness and increases in heart rate. The utility of study CVT 5111 is limited: There were only 35 subjects who completed the trial – all of whom were healthy, non-smoking males and there were only 8 subjects each in the 20 microgram/kg and 30 microgram/kg cohorts.
Trials CVT 5121 and CVT 5122 have been reviewed in section 1.3.2. The reviewer has already described the process leading to the choice of 400 micrograms as the dose to be used in the Phase 3 clinical trial and dose recommended to be used in clinical practice. At the dose of 400 mcg the APV was ≥ 2 times normal for ≥2.5 minutes. This dose appears appropriate but its effect on large groups of patients with decreased left ventricular function or bronchorestrictive and bronchospastic lung disease are not known.

Reviewer's Comment: As a result of the sponsor choice of subjects, study CVT 5111 has not adequately found MTD in the relevant group of patients who would be receiving Lexiscan – namely patients with possible coronary artery disease and an additional associated disorder such as hypertension or nicotine abuse. In study 5122, the ability of Lexiscan to increase APV to ≥ 2 times normal has not been adequately demonstrated in patients with diminished left ventricular function or patients with common forms of lung disease – both groups also likely to receive this agent in clinical practice.

1.3.5 Drug-Drug Interactions

Clinical trial CVT 5123 was a double-blind, randomized, crossover trial to evaluate the effect of oral caffeine or Lexiscan-induced increases in myocardial blood flow as monitored by positron emission tomography in normal volunteers. While there was no change in coronary flow rate (CFR) detected in the trial, the trial does not rule out nor does it establish a significant interaction between Lexiscan and caffeine. 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 >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 Lexiscan on CFR by sex.
Additional findings from this trial: Lexiscan-induced headache severity was decreased with caffeine. Caffeine attenuated the HR increase caused by Lexiscan. After Lexiscan 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.

1.3.6 Special Populations

This product has a pediatric waiver. Subjects dosed with Lexiscan (Set 1) were a mean of 62.2 years of age (range of 19-93 yr) with 38% between 45 and 64 years of age and 21% over 75 years of age. The majority of subjects in Set 1 was male (70%), Caucasian (78%), and enrolled in the United States or Canada. On the day of dosing, the subjects had a mean weight of 83.2 kg (range 42.0-161 kg), 7% had a weight <60 kg, and the mean BMI was 28.7 kg/m2 (range 16.4-56.7 kg/m2). The Set 2 patients who received blinded Lexiscan were a mean of 65.6 years of age and the majority ranged from 45 to 74 years of age (72%). The majority were Caucasian (76%), North American (60%), overweight (mean BMI of 29.2 kg/m2), and male (70%) with reasonable kidney function (83% had CLcr≥50 ml/min).
Reviewer's Comment: The majority of patients receiving Lexiscan were old, obese Caucasian males. Hence, there is more limited information on the effects of Lexiscan on the non-Caucasian and female population. In the Lexiscan groups 69% of the patients had a Diamond/Forrester (method to calculate probability of coronary artery disease) pre-test probability of coronary artery disease ≥90.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

- Myocardial Perfusion Stress Agent ; augmenter of coronary artery blood flow
- Established name: regadenoson; Proposed trade name: Lexiscan
- Chemical class: adenosine A_{2A} receptor agonist; new molecular entity

- Pharmacological class: Pharmacologic stress agent
- Proposed indication [redacted]

2.2 Currently Available Treatment for Indications

Adenosine marketed as adenoscan is the only other agent available in the United States for the same indication.
Dipyridamole marketed as Persantine under NDA 19-817 was approved in December, 1990. The NDA was withdrawn in 2003 for marketing reasons.

2.3 Availability of Proposed Active Ingredient in the United States

Lexiscan contains no active ingredient that is already marketed in the United States.

2.4 Important Issues with Pharmacologically Related Products

Safety concerns with adenosine in postmarketing experience are: the development of atrio-ventricular block and the induction of bronchospasm.Fatal cardiac arrest, sustained ventricular tachycardia (requiring resuscitation), and nonfatal myocardial infarction have been reported coincident with Adenoscan infusion. Patients with unstable angina may be at greater risk.

The following are the Adverse Events associated with adenosine in the study patients:

Approximately 2.6% and 0.8% of patients developed second- and third-degree AV block, respectively. All episodes of AV block have been asymptomatic, transient, and did not require intervention; less than 1% required termination of adenosine infusion.

Adverse reactions that were seen most often included flushing (44%), chest discomfort (40%), and dyspnea (28%). Adverse reactions usually resolve quickly when infusion is terminated and generally do not interfere with test results.

Despite adenosine's short half-life, 10.6% of the adverse events started several hours after the infusion terminated, and 8.4% of the adverse events that began during the infusion persisted for up to 24 hours after infusion. In many cases, it is not possible to know whether these late adverse events are the result of Adenoscan infusion.

2.5 Presubmission Regulatory Activity

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 CVT and the Agency were held to discuss and reach agreement on the Chemistry, Pharmacology/Toxicology and Clinical aspects of the program. Key agreements are cited in the NDA and copies of meeting minutes are provided as reference documents.

Responsibility for the regadenoson IND was transferred from DCRP to the Division of Medical Imaging and Hematology Products (DMIHP) on 01 September 2006. Since then, an End of Phase 3 Meeting and a Pre-NDA Teleconference in February 2007 with DMIHP confirmed previous agreements on the development program and the acceptability of the clinical data package for submission in an NDA; general agreement was also reached on the proposed format and content for the clinical portion of the NDA submission.

Date	Description of Meeting, Discussion or Agreement
26 Jul 2002	Clinical Development Plan Meeting with DCRP and DMIRDP: general agreement on use of image-to-image non-inferiority approach for Phase 3
11 Jul 2003	End of Phase 2 Meeting with DCRP and Statistics lead from DMIRDP: agreement on specific aspects of Phase 3 design and analysis; other agreements on clinical program
06 Aug 2003	Teleconference with DCRP: agreement on use of ^{99m}Tc and dual isotope protocols for Phase 3
12 Sep 2003	Teleconference with DCRP: agreement on plan for adjustment for multiplicity in the analysis of the secondary safety and tolerability endpoints for Phase 3
11 Mar 2004	Statistical Analysis Plan for Phase 3 Study CVT 5131 reviewed by Dr. James Hung (DCRP)
31 Mar 2004	Written advice (email from Russell Fortney) from Division of Pulmonary Drug Products on design of asthma / COPD studies
22 Oct 2004	Full pediatric waiver granted by DCRP for regadenoson as an adjunct to radionuclide MPI
14 Dec 2004	Teleconference with DCRP: discussion of caffeine interaction study design (CVT 5123) and implications for product labeling
24 Aug 2005 07 Sep 2005	Dr. James Hung (DCRP) agreement (emails from Russell Fortney) with increase in sample size for CVT 5131 (Amendment VI)
01 Feb 2007	End of Phase 3 Meeting with DMIHP: (1) confirmation of previous agreements with Sponsor regarding Phase 3 study design, and (2) data summarized by Sponsor support submission of an NDA
06 Feb 2007	Pre-NDA Teleconference with DMIHP: agreement regarding (1) Data from CVT 5125 and CVT 5126 will be integrated in 4-mo safety update, (2) plan for integrated efficacy and safety analyses, summaries, and datasets, (3) general eCTD/NDA format, (4) case report forms and data tabulations. DMIHP (1) asked to review eCTD test submission, (2) requested special efficacy dataset for NDA, and (3) provided specifications for population PK/PD datasets.

DCRP = Division of Cardiovascular and Renal Products

DMIRDP = Division of Medical Imaging and Radiopharmaceutical Drug Products

DMIHP = Division of Medical Imaging and Hematology Products, formerly DMIRDP

In a letter from the DCRP dated 22 October 2004, CVT was granted a pediatric waiver for all pediatric age groups for use of Lexiscan in the proposed indication.

2.6 Other Relevant Background Information

No reports of regulatory actions in other countries are provided in the NDA document.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

No findings relevant to the clinical review.

3.2 Animal Pharmacology/Toxicology

Lexiscan at doses higher than the clinical dose induced minimal cardiomyopathy (isolated myocyte necrosis and inflammation) in rats. The cardiomyopathy induced by Lexiscan was associated with hypotension and was reversible. Profound hypotension induced by vasoactive drugs is known to induce cardiomyopathy in rats. This finding therefore does not raise clinical concerns (see FDA primary and consultative toxicology reviews for details).

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The source of data for this review comes from the results of clinical trials, Phase 1- 3, performed by the sponsor. Aspects of the NDA, such as the pre-clinical data suggestive of a rat cardiomyopathy, have been discussed with the Cardio-Renal Division within CDER.

4.2 Tables of Clinical Studies

Protocol Number Study Status Study Dates	Study Design Objective Primary Endpoint	Number of Subjects	Healthy Subjects or Patients	Treatment/Dosage Form/Duration of Treatment/Dose Regimen (n), Route
Human PK Studies				
Healthy Subject PK and Initial Tolerability				
CVT 5111 Status: Completed Start Date: Nov 2000 Completion Date: Mar 2001	Design: double-blind, randomized, placebo-controlled, crossover, ascending single-dose study. Objective: to determine the MTD of Lexiscan following iv administration while the subject was supine and again while standing; and to determine the PK of iv Lexiscan. Primary endpoint: safety assessment and determination of the MTD.	Enrolled: 42 Dosed: 36 Completed: 35	Healthy male subjects	Lexiscan Injection (0.1, 0.3, 1, 3, 10, 20, and 30 mcg/kg) or matching Placebo Injection via iv bolus given over 20 sec, while supine and again while standing (all doses, except 30 mcg/kg, were evaluated in the standing position). There were 4 subjects in each of the 0.1, 1, 3, 10, and 30 mcg/kg dose groups, and 8 subjects in the 0.3 and 20 mcg/kg dose groups.

Protocol Number Study Status Study Dates	Study Design Objective Primary Endpoint	Number of Subjects	Healthy Subjects or Patients	Treatment/Dosage Form/Duration of Treatment/Dose Regimen (n), Route
Renal Patients PK				
CVT 5112 Status: Completed Start Date: Dec 2004 Completion Date: Mar 2005	Design: open-label, single-dose study. Objective: to investigate the relationship between renal function and Lexiscan clearance. Primary endpoint: PK of Lexiscan in subjects with varying degrees of renal impairment.	Enrolled and dosed: 24 Completed: 24 Number by renal impairment group: None 6 Mild 7 Moderate 6 Severe 5	Normal subjects and subjects with mild, moderate, and severe renal insufficiency	Lexiscan Injection, single 400 mcg iv bolus within 10 sec (n = 24).

Protocol Number Study Status Study Dates	Study Design Objective Primary Endpoint	Number of Subjects	Healthy Subjects or Patients	Treatment/Dosage Form/Duration of Treatment/Dose Regimen (n), Route
Human PD Studies				
Healthy Subject PD and PK-PD				
CVT 5123 Status: Completed Start Date: Mar 2005 Completion Date: Jul 2005	Design: double-blind, randomized, crossover study. Rest and stress MBF were measured by PET in the presence and absence of caffeine. Objective: to evaluate the effect of a 200 mg oral dose of caffeine on the Lexiscan-induced increase in MBF measured 2 h after ingestion. Primary endpoint: CFR, defined as the ratio of stress (post-Lexiscan) MBF to rest (baseline) MBF.	Enrolled: 45 Dosed: 43 Completed: 41	Healthy subjects	Lexiscan Injection, 400 mcg iv bolus within 10 sec. Subjects received a total of 2 doses, separated by a 1–14 day washout period (n = 41). Caffeine, 200 mg, or matching placebo, po, approximately 100 min prior to Lexiscan dosing. On the 2 dosing days, subjects received caffeine on one day (n = 41) and the matching placebo (n = 43) on the other day.

Protocol Number Study Status Study Dates	Study Design Objective Primary Endpoint	Number of Subjects	Healthy Subjects or Patients	Treatment/Dosage Form/Duration of Treatment/Dose Regimen (n), Route
Patient PD and PK-PD				
CVT 5121 Status: Completed Start Date: Sep 2001 Completion Date: Jan 2005	Design: open-label, single-dose study; conducted in 3 parts: *Part A*: single-dose escalation to identify a well-tolerated dose that would increase APV of CBF ≥ 2-times that of baseline for at least 2 min. *Part B*: single 30 mcg dose in subjects with reduced LVEF to assess PK and safety. *Part A1*: single 400 mcg dose, followed 1 min later by 100 mg of aminophylline to assess whether aminophylline antagonized the effects of Lexiscan. Objective: to identify an optimal dose regimen of Lexiscan that would cause a ≥ 2-fold increase in APV of CBF above baseline that would last at least 2 min. Primary endpoint: the time that the ratio of APV of CBF (following Lexiscan dosing) to baseline APV was at least 2.	Enrolled: 41 Dosed: 40 Completed: 40 Number dosed within each part of the study: Part A 34 Part B 2 Part A1 4	Subjects undergoing a clinically-indicated cardiac catheteriza-tion	Lexiscan Injection, single iv bolus within 10 sec. Doses varied by study part: Part A dose # subjects 10 mcg 4; 30 mcg 4; 100 mcg 4; 300 mcg 7; 400 mcg 9; 500 mcg 6. Part B 30 mcg 2 ; Part A1 400 mcg 4. In Part A1 (only), 1 min following Lexiscan Injection, subjects received a single iv injection of 100 mg aminophylline, given over 60 sec.

Protocol Number Study Status Study Dates	Study Design Objective Primary Endpoint	Number of Subjects	Healthy Subjects or Patients	Treatment/Dosage Form/Duration of Treatment/Dose Regimen (n), Route
CVT 5124 Status: Completed Start Date: Mar 2005 Completion Date: Oct 2005	Design: double-blind, randomized, placebo-controlled, crossover study. Objective: to compare the incidence of bronchoconstrictive reactions (i.e., a reduction from baseline FEV1 of > 15%), within 2 h after dosing with a 400 μg Lexiscan iv bolus to that following a placebo bolus. Primary endpoint: the incidence of bronchoconstrictive reactions.	Enrolled and dosed: 48 Completed: 47	Subjects with AMP-sensitive mild or moderate asthma	Lexiscan Injection, single 400 mcg iv bolus within 10 sec (n = 47) Placebo Injection, iv bolus within 10 sec (n = 48) The two treatments were separated by a 1–14 day washout period.
CVT 5125 Status: Completed Start Date: Feb 2006 Completion Date: Sep 2006	Design: double-blind, randomized, placebo-controlled, crossover study. Objective: to assess the overall safety of Lexiscan. Primary endpoint: safety, including spirometry measures (including a reduction from baseline FEV1 of > 15%), and signs, symptoms and treatment for bronchoconstriction.	Enrolled and dosed : 49 Completed: 49	Subjects with moderate and severe (Stages II and III) COPD	Lexiscan Injection, single 400 mcg iv bolus within 10 sec (n = 49). Placebo Injection, single iv bolus within 10 sec (n = 49). The two treatments were separated by a 7–14 day washout period.

Protocol Number Study Status Study Dates	Study Design Objective Primary Endpoint	Number of Subjects	Healthy Subjects or Patients	Treatment/Dosage Form/Duration of Treatment/Dose Regimen (n), Route
Efficacy and Safety				
Controlled Clinical Studies Pertinent to the Claimed Indication				
CVT 5131 Status: Completed Start Date: Oct 2003 Completion Date: Aug 2006	Design: double-blind, double-dummy, randomized trial. Patients had a baseline stress scan acquired with adenosine and were then randomized 2:1 to a second stress scan acquired with Lexiscan or adenosine, respectively. Objective: to demonstrate that the strength of agreement between Lexiscan and adenosine images was not inferior to the strength of agreement between two sequential adenosine images; and to compare the safety and tolerability of Lexiscan to that of adenosine. Primary endpoint: the median count across 3 independent readers of the number of segments (in the 17-segment model) having reversible defects.	Number Dosed:1231 Completed: 1211 Regadeno-son: 808 Adenosine: 403	Patients referred for a clinically-indicated pharmaco-logic stress SPECT MPI study	Lexiscan Injection, single 400 mcg iv bolus within 10 sec, and placebo adenosine solution, iv infusion over 6 min (n = 820). Adenosine Injection (Adenoscan), iv infusion at 140 mcg/kg/min over 6 min, and Placebo Injection, single iv bolus within 10 sec (n = 411).

Protocol Number Study Status Study Dates	Study Design Objective Primary Endpoint	Number of Subjects	Healthy Subjects or Patients	Treatment/Dosage Form/Duration of Treatment/Dose Regimen (n), Route
CVT 5132 Status: Completed Start Date: Apr 2004 Completion Date: Jun 2005	Design: double-blind, double-dummy, randomized trial in patients referred for a clinically-indicated pharmacologic stress SPECT MPI study. Patients had a baseline stress scan acquired with adenosine and were then randomized 2:1 to a second stress scan acquired with Lexiscan or adenosine, respectively. Objective: to demonstrate that the strength of agreement between Lexiscan and adenosine images was not inferior to the strength of agreement between two sequential adenosine images; and to compare the safety and tolerability of Lexiscan to that of adenosine. Primary endpoint: the median count across 3 independent readers of the number of segments (in the 17segment model) having reversible defects.	Number Dosed: 787* Completed: 784 Regadeno-son: 517 Adenosine: 267 * 3 patients terminated prematurely because of infusion pump failure and no safety data were obtained	Patients referred for a clinically-indicated pharmacolog ic stress SPECT MPI study	Lexiscan Injection, single 400 mcg iv bolus within 10 sec, and placebo adenosine solution, iv infusion over 6 min (n = 519). Adenosine Injection (Adenoscan), iv infusion at 140 mcg/kg/min over 6 min, and Placebo Injection, single iv bolus within 10 sec (n = 268).

Protocol Number Study Status Study Dates	Study Design Objective Primary Endpoint	Number of Subjects	Healthy Subjects or Patients	Treatment/Dosage Form/Duration of Treatment/Dose Regimen (n), Route
CVT 5126 Status: Completed Start Date: May 2006 Completion Date: Nov 2006	Design: double-blind, randomized, placebo-controlled study. All patients had a 6-min supine adenosine MPI, followed 1–7 days later by an MPI obtained using ETT (4-min treadmill walk at a rate of 1.7 miles per hour with 0% incline) and either Lexiscan or placebo (administered 90 sec after the start of ETT). Objective: to assess the overall safety of Lexiscan. Primary endpoint: safety as assessed by BP, HR, cardiac rhythm, and AEs.	Enrolled: 62 Randomized: 60 Lexiscan: 39 Placebo: 21	Patients requiring an MPI and able to perform low level exercise	Lexiscan Injection, single 400 mcg iv bolus within 10 sec (n = 39). Placebo Injection, single iv bolus within 10 sec (n = 21).

Protocol Number Study Status Study Dates	Study Design Objective Primary Endpoint	Number of Subjects	Healthy Subjects or Patients	Treatment/Dosage Form/Duration of Treatment/Dose Regimen (n), Route
Uncontrolled Clinical Studies				
CVT 5122 Status: Completed Start Date: Aug 2002 Completion Date: Jan 2003	Design: open-label, pilot study to evaluate Lexiscan as a pharmacological stress agent for MPI. Objective: to select a dose of Lexiscan that resulted in SPECT MPI images similar to those acquired with adenosine as the stress agent. Primary endpoint: the presence or absence of ischemia, determined by consensus of 3 readers, blinded to patient identity and stress agent.	Enrolled and Dosed: 36 Completed: 36	Patients with a clinically-indicated pharmaco-logic stress SPECT MPI study showing predomin-antly reversible perfusion defects	Lexiscan Injection, single iv bolus of 400 mcg (n = 18) or 500 mcg (n = 18), within 10 sec.

4.3 Review Strategy

The general review strategy was to review the clinical trials presented by the sponsor. The data was reviewed independently of the summaries provided by the sponsor. All relevant trials supportive of efficacy were reviewed.

4.4 Data Quality and Integrity

The Division of Scientific Investigations (DSI) was asked to inspect 3 sites. [redacted] was to be inspected because it had a large number of patients in one Phase 3 trial. [redacted] and [redacted] also was to be inspected due to their large patient enrollments in the Phase 3 trials.
DSI also inspected the central reading facility [redacted] and the sponsor's headquarters in Palo Alto, California. At the clinical sites the inspectors noted some protocol deviations. The inspections of the reading facility and headquarters dealt with assurance of the data's integrity.

Foreign Clinical Sites

[redacted] : For study CVT 5131 221 patients were consented and 90 patients completed the random scan; for study CVT 5132 54 patients were consented and 28 completed the random scan. At the [redacted] :: For study CVT 5131, 120 patients were consented and 48 completed the random scan. For study CVT 5132, 47 patients were consented and 36 completed the random scan. For both of these sites, there were minor deviations such as a female patient who did not have a pregnancy test. However, overall the data was deemed acceptable by DSI.

United States Clinical Site

Concerns arouse when the inspector noted that the pharmacist was mixing the psa agent for the random scan on the night before the nuclear scan study. The sponsor provided documentation that the psa agent would be stable in a syringe overnight. Several other deviations were also reported. The full report from DSI is not complete at the time of this writing. This reviewer reviewed the medical chart of an elderly participant that ultimately succumbed to complications from a cardiac catheterization following participation in a Phase 3 study and concurs with the earlier conclusion that the participant's death was not related to the study agent. However, from the information currently available this reviewer believes the protocol deviations found at the clinical site are relatively minor and the data from the site could be accepted.

Central Facilities

DSI also inspected the central nuclear scan reading facility [redacted] Following detailed review of the reading process and the physical setup of the facility, no concerns were raised about the integrity of the data.
The sponsor's headquarters in Palo Alto, California was inspected and their files were reviewed. No evidence was found that the sponsor had early or inappropriate access to the data coming from the [redacted] reading facility. Based on these reports, the integrity of the data is intact and appropriate for meaningful review by FDA.

4.5 Compliance with Good Clinical Practices

In the two Phase 3 trials, CVT-5131 and CVT-5132, protocol violations occurred 312 (78%) and 224 (84%) times respectively in the adenosine patients and 666 (81%) and 427 (83%) times respectively in the Lexiscan patients. Deviations primarily involved the timing (ie, not collected within a specified time window) or performance (ie, not performed or not recorded) of the safety and tolerability assessments.
In study CVT 5131 deviations regarding ECG assessments were most frequently noted (35% in each group) primarily resulting from ECG collection outside the specified windows (20% adenosine, 21% Lexiscan). In both Phase 3 trials deviations regarding vital sign assessments were frequently noted and particularly prior to dosing with the randomized stress agent. Imaging timing deviations (16% adenosine and 20% Lexiscan in CVT 5131) occurred with about equal frequency in both studies. These deviations primarily consisted of the imaging starting <60 minutes or >90 minutes from the radionuclide injection for the initial adenosine stress scan and the randomized stress scan. Deviations regarding caffeine or theophylline levels occurred in 16% of adenosine and 18% of Lexiscan patients in study CVT 5131 and with about equal frequency in CVT 5132. These deviations included plasma levels above the designated thresholds (caffeine: 3mcg/ml; theophylline: 0.25 mcg/ml) before the initial adenosine scan and deviations regarding the collection of blood samples for caffeine and theophylline determination.

No ethical issues were identified

4.6 Financial Disclosures

The sponsor provides acceptable financial disclosure information.

5 CLINICAL PHARMACOLOGY

No issues to be addressed by the clinical reviewer were identified.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Lexiscan is indicted for use as a pharmacologic stress agent in conjunction with nuclear cardiac scans. This agent is to be given to patients who are incapable of exercising adequately to increase their coronary blood flow during a nuclear cardiac scan.

6.1.1 Methods

As noted in section 4.1 the primary source for the Lexiscan efficacy data comes from the two Phase 3 trials, CVT 5131 and CVT 5132. Both of these trials were identical in design and execution.

6.1.2 General Discussion of Endpoints

The endpoint is for the phase 3 study is a non-inferiority margin: that the mean differences between the scores of an adenosine vs. Lexiscan scans not exceed the difference between two adenosine scans by a pre-specified amount. The derivation of the quantification of the difference between adenosine/Lexiscan vs. adenosine/adenosine will be described in the statistical section. The limitation of this comparison is based on the validity of the derivation of an acceptable level of difference. The level of difference is derived from a kappa value and the appropriateness of kappa as a mechanism of comparison will be discussed in the statistical section.
The sponsor makes the following non-inferiority claim:
Lexiscan-Adenosine agreement minus Adenosine-Adenosine agreement > -13.3%
The sponsor justified this value limit through analogies with the kappa statistics where the literature suggests a 20% difference in kappa as a significant difference. The sponsor argued that the 13.3% difference for his measure corresponds to a 20% kappa difference. The analogies are weak, but the limit was acceptable.
The blinded readings for the Comparator arm – Adenosine/Adenosine – and for the Test arm – Adenosine/Lexiscan – each provided a pair of classifications: (Initial perfusion defect category, Randomized perfusion defect category) for each patient, where the classes could be low, moderate or high. The statistics revealed that the two study arms presented the same distribution for these pairs of classifications. (For example, the percentage of patients in the Adenosine/Adenosine arm with a low number of perfusion defects on the initial scan, and a moderate number of perfusion defects on the randomized scan was essentially the same as the percentage of patients in the Adenosine/Lexiscan with a low number of perfusion defects on the initial scan and a moderate number of perfusion defects on the randomized scan.) Having this constancy across study arms for all pairings of initial and randomized scan reads provides additional support to the sponsor's claim of non-inferiority of Lexiscan to adenosine.
The endpoint was assessed by having three independent readers interpret the nuclear scans; their readings done under the auspices of an IRC. The secondary endpoints for these Phase 3 studies were:

- Paired comparison of initial adenosine and randomized scans with respect to the amount of ischemia
- Agreement by Diamond and Forrester pretest probability of Coronary Artery Disease
- Summed Stress Score, as derived via reader interpretation and by software (4D-MSPECT)
- Image quality and sub diaphragmatic interference
- Overall findings (diagnostic certainty) and diagnostic category (patient diagnosis)
- Transient ischemic dilation, lung uptake, and wall motion

6.1.3 Study Design

The Phase 3 trials were conducted within the regulations of an adequate and well-controlled study.
The study design called for the patient during the randomized scan (receiving either adenosine or Lexiscan) to have two IVs – one for an infusion which could be adenosine (or placebo) and one for an injection of Lexiscan (or placebo). Given the nature of the Phase 3 study design, the endpoint was well defined – the patient having completed two sets of nuclear scans – one of which was adenosine and the other was either Lexiscan or adenosine chosen at random in a 2:1 (Lexiscan:adenosine) ratio. For the random scan, the patients who received adenosine had characteristics similar to those who received Lexiscan. The adenosine/adenosine patients served as the active control group.
The sponsor enriched the Phase 3 studies with patients that had ischemic cardiac disease based on the initial adenosine scan. After selection of 100 patients with 0-1 segments of ischemia on the initial scan, the studies were closed to prospective patients with this low level of ischemia. Hence at the clinical research sites, local investigators had some idea of the type of patients that were involved in the bulk of the Phase 3 studies. Thus the overwhelming majority of patients (76% Adenosine, 73% Lexiscan for CVT 5131; 59% Adenosine, 63% Lexiscan for CVT 5132) fell into the high risk category for coronary artery disease on the Diamond-Forester scale.
The study population consisted overwhelmingly of Caucasian, older males (55% ≥65 years). Patients with concomitant lung disease were excluded from the study. The rationale for the exclusion was based on the labeling for adenosine which recommends adenosine not be used in the presence of lung disease. Since all of the Phase 3 patients would definitely be receiving adenosine, patients with lung disease were excluded. This exclusion obviously limits our knowledge of the action of Lexiscan in patients with lung disease. This reviewer suspects that in clinical practice physicians will chose Lexiscan as an alternative for adenosine in patients with concomitant lung disease requiring a nuclear cardiac scan as part of a clinical evaluation. This choice will be made without detailed information on the effect of Lexiscan on a large population of patients with lung disease.
The rationale for the test dose of Lexiscan was reviewed earlier in this report. There is little Information on the changes in coronary artery blood flow in patients with decreased left ventricular function. In study CVT 5131 and CVT 5132, 10% and 6% of the patients respectively, had ejection fractions below 35%.

6.1.4 Efficacy Findings

The primary measure for the non-inferiority test of Lexiscan vs. adenosine was based on the number of segments showing ischemia using a 17-segment model of the heart. The number of ischemic segments is a measure of the extent of ischemia and the reader must: differentiate ischemia (perfusion defects present only during stress) from infarct (perfusion defects present at both rest and stress) and from normal myocardium (no perfusion defects at rest or stress).
Each reader scored the 17 anatomical segments on both the rest and stress images using a clinically accepted 5-point semi-quantitative scale for radiotracer uptake as follows: 0=normal; 1=mildly reduced or equivocal; 2=moderately reduced; 3=severely reduced; or 4=absent uptake.

A particular segment was counted as showing reversible ischemia if the stress score was greater than the rest score and stress score was at least 2 (moderately reduced). The requirement for an ischemic segment to have a stress score of at least 2 was applied to ensure that mild or equivocal perfusion defects were not included in the determination of ischemia because these may be attributable to artifact, tracer inhomogeneity or clinically unimportant ischemia.
The median count across the three readers of the number of segments with reversible ischemia was categorized as follows:

- 0-1 segments with reversible ischemia = no ischemia
- 2-4 segments with reversible ischemia = small to moderate ischemia
- 5-17 segments with reversible ischemia = large ischemia

For calculation of non-inferiority, the sponsor took the median assessment of ischemia across three readers and likened it to taking the majority opinion among three readers. The number of segments with reversible ischemia with at least a moderate reduction in perfusion (level 2=moderately reduced) reflects the amount of myocardium at risk which is commonly used to guide clinical decisions. The three categories were chosen to represent patients for whom medical management is indicated (0-1), patients for whom revascularization may be indicated (2-4), and patients requiring urgent intervention if their condition permits (≥5).
Data for image analyses was specified in the CVT 5131 and CVT 5132 protocols as the Restricted Analysis Set (RAS), comprising all patients who were dosed with blinded study medication, whose initial adenosine studies and randomized studies were scored by the readers, and, if enrolled after closure of randomization to patients assessed at the sites as having initial adenosine studies showing fewer than 2 segments with reversible defects, also had randomized studies assessed at the sites as showing at least 2 segments with reversible defects. An overview of the combined efficacy data from CVT 5131 and CVT 5132 can be summarized as the following:

- The patients in both Phase 3 studies were typical of cardiac patients referred for stress imaging, with patients with greater disease severity over-represented by design. The study population included a high percentage of patients with a history of significant co-morbidities including previous MI, unstable angina, coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI), congestive heart failure (CHF), cardiac arrhythmias and diabetes.
- The primary endpoint was achieved demonstrating that Lexiscan is not inferior to adenosine in assessing the extent of reversible perfusion abnormalities. The combined estimated difference of agreement rates between adenosine-Lexiscan and adenosine-adenosine is 0% with 95% confidence limits of -6.2% to =6.8%. Agreement rates for the secondary image analyses are similar for the two stress agents.
- Agreement rates were also similar for the two stress agents in subgroups defined by age, gender, BMI, history of diabetes, ejection fraction, and imaging protocol used. Smaller sample sizes and variable distribution of ischemic segments within each subgroup limited comparisons made by race, pretest probability of coronary artery disease, geography and use of concomitant medications, but agreement rates within each of these subgroups were also broadly consistent for the two agents.
- For both Lexiscan and adenosine, women had lower agreement rates when ≥2 reversible segments were noted on the initial scan.

In study CVT 5131, using the median assessment of the number of reversible defects from the 3 readers, the average agreement rate with respect to ischemia size category between the initial study and the adenosine-obtained images during the randomized study was 0.61±0.02. The difference between these two rates is 0.01±0.04 (95% CI=-0.075, 0.092). The lower limit of the 95% CI is above the non-inferiority margin of -0.133, demonstrating that the reading Lexiscan vs. adenosine images differences fit within the limits pre-specified by the sponsor.
For both stress agents, the data are compatible with the hypothesis that the proportions in the three ischemia size categories 0-1, 2-4, and ≥5 reversible segments are the same for the initial adenosine study and the randomized study. Thus, there is no evidence of a shift in the assessed extent of ischemia between the initial and randomized scans.
For the individual studies and combined analysis, agreement rates between initial adenosine and randomized Lexiscan were higher when only 0-1 segments were noted on the initial scan, compared to the other ischemic size categories. In CVT 5131, agreement rates were slightly higher for the "small to moderate" (2-4 reversible segments) than the "large category" (≥5 reversible segments) category; whereas, in CVT 5132 agreement rates were slightly higher for the "large" category, relative to the "small to moderate" category. In the combined analysis, agreement rates were similar for both categories. Lower agreement rates in the larger ischemia categories can be explained by the fact that interpretation of ischemia is subject to a larger number of sources of variability. Thus, with increasing degrees of ischemia, agreement can be expected to become somewhat lower. (Table 3)
In CVT 5132, for both Lexiscan and adenosine, an upward shift in the extent of ischemia (0-1, 2-4, and ≥5 reversible segments) was seen from the initial to the randomized study. The shift appeared to be present for each of the three individual readers and for both stress agents, and also appears to have been present both before and after closure to the "no ischemia" size category. The cause of the shift is unknown.
Secondary imaging analyses were performed in order to further evaluate Lexiscan vs. adenosine with respect to detection of ischemia and image quality.
Paired (side-by-side) comparison of ischemia extent: Readers were shown a display, including the stress images from both studies, with the stress images from the second study randomly assigned to position 1 or position 2, as well as the rest images from the first study. The readers rated the study in position 1 as showing more ischemia, less ischemia or the same extent of ischemia. A Cochran-Mantel-Haenszel test of equality of mean scores (adenosine and Lexiscan) was performed, where scores were Less=-1, Same=0 and Greater=1.
For the combined RAS of the two Phase 3 trials, agreement of the first and second studies with respect to ischemia size category for patients in each of the three Diamond and Forrester categories (<10%, 10-90%, and >90%), was summarized by randomized stress agent. For each of the categories, both randomized stress agents had similar agreement rates. Similar agreement rates (weighted average) were also observed across all three Diamond and Forrester categories.
For software and reader SSS, category agreement rates between the adenosine and Lexiscan images were similar for the individual studies and the combined studies. For CVT 5131 and CVT 5132 and the combined studies, reader and software SSS were comparable for all SSS categories for both stress agents. Agreement rate for reader SSS in CVT 5131 was higher than CVT 5132 for each of the SSS categories. This is likely to be due to the use of different readers for the two trials and possibly also slightly better image quality obtained in CVT 5131. In

addition, for the combined and individual trials, agreement rates were higher for software and reader SSS categories of 0-3 and ≥12 for both stress agents. This difference is likely to be due to less variable segment scoring for patients with no or minimal stress perfusion defects (0-3) and with severe or extensive stress perfusion defects.

For CVT 5131 and CVT 5132 and the combined analysis, most randomized stress images were of good to excellent quality and proportions rated good or excellent were comparable between the randomized adenosine and Lexiscan groups. Stress image quality was better in CVT 5131 than CVT 5132 for both randomized stress agents and for the initial adenosine scans, which may account for better agreement rates in CVT 5131. The difference may be due to reader interpretation differences, or actual differences in the quality of the images. Because the proportion of patients were similar with respect to gender and BMI>30 kg/m^2 any differences in actual quality are more likely to be due to variability in equipment quality or imaging acquisition or processing methods used by sites between the two studies than to patient factors.

In CVT 5131 and CVT 5132 and the combined trials, there was no apparent sub diaphragmatic interference in the majority of images (≥90%) obtained with either stress agent. In each of the individual studies, and in the combined analysis, there were similar amounts of sub diaphragmatic interference for both treatment groups for the initial and randomized stress scans.

Agreement with Respect to Overall Findings – Diagnostic Certainty. Lexiscan and adenosine were similar when comparing the agents with respect to overall findings (normal vs. abnormal). Agreement was generally higher for the "normal" ischemia category in both studies, while agreement was generally lower for the "abnormal" ischemia category. For the individual studies and combined analysis, overall average agreement rate by diagnostic categories of "normal", "ischemia", "ischemia+scar", or "scar" and average agreement by coronary artery territory were similar for both stress agents. Agreement rates for each diagnostic category were also similar, although the agreement rates were highest in the "normal" category and lowest when "ischemia" or "scar" alone is present. As discussed previously, agreement rates are generally higher when the scan is "normal" when no ischemia is present. A possible reason for the lower agreement rates in the diagnostic category of "scar" alone despite the absence of ischemia is that defects considered by some readers as artifact due to attenuation may be considered by others as a scar (infarct).

Assessment of Transient Ischemic Dilation (TID), Lung Uptake and Wall Motion Most patients had no apparent TID on either the adenosine or randomized scan in the Phase 3 trials. In patients randomized to adenosine, no lung uptake was seen in randomized stress images. In patients randomized to Lexiscan, slight lung uptake was seen in 7 of 1240 randomized stress images (<1%). For both stress agents, wall motion abnormalities were similar in location and severity between the initial and randomized scan for both Phase 3 trials.

Comparison to Angiography Angiography reports were collected when available within 12 weeks of the randomized scan. Angiography can be considered the ultimate gold standard for the recognition of coronary artery lesions. For the combined trials, angiography results were available for 26% of patients with abnormal initial studies and 10% of patients with normal initial studies. The referral for angiography was probably influenced in many cases by clinical assessments beyond the study and the patient's medical history. Only patients who had angiography performed, and who were clinically stable between the initial and/or randomized scan and the date of angiography were included in the Angiography Analysis Set. Angiograms

were considered abnormal when ≥70% stenosis was present in one or more of the three main coronary arteries (LAD, LCx, and RCA) or their branches and/or bypass grafts.
Agreement of randomized study results with angiography results was summarized in three ways: (1) by counting the randomized study as positive when the diagnostic category was definitely or probably abnormal and as negative when the category was equivocal or definitely or probably normal; (2) by presenting proportions of positive studies for patients with angiograms and 1-,2-, and 3-vessel disease; and (3) by coronary artery territory, counting the randomized study as positive when the median assessment for the territory was ischemia or ischemia+scar and as negative when the median assessment for the territory was normal or scan.
For the individual studies, the Angiography Analysis Set (n=399) was used. This comprised patients in the Efficacy-Evaluable Analysis Set (EAS) for whom angiography results were obtained within 100 days of the randomized study who had been judged prior to unblinding by the Protocol Deviation Classification Committee not to have had a change in clinical status that would invalidate the comparison. For the combined trials, and post unblinding, a more inclusive analysis set was also used. This special analysis set added patients who had been excluded from the EAS but who had angiography results obtained within 100 days where the site indicated that there had been no change in clinical status (n=456). For both analysis sets, sensitivity and specificity for Lexiscan was comparable to adenosine. (Table 5)

6.1.5 Efficacy Conclusions

The data presented in the primary and secondary analyses, support the conclusion that Lexiscan MPI is not inferior to adenosine MPI in assessing the extent of reversible perfusion abnormalities. The agreement rates for the secondary analyses are similar between Lexiscan and adenosine. These secondary analyses include analyses of Reader and Computer SSS, Overall Findings, Diagnostic Categories, Presence or Absence of Ischemia and Paired Comparisons of Ischemic extent. Compared to angiography, the estimated sensitivity and specificity of Lexiscan and adenosine are similar; however the number of patients undergoing cardiac angiography was small. The agreement rates for Lexiscan and adenosine was similar over multiple subgroups of patients and medical conditions. Any of the other secondary analyses performed by the sponsor are of limited clinical importance and utility.
Therefore the sponsor has presented data which support the use of Lexiscan as a psa. The data are limited since most of the study participants were older Caucasian males. More information is needed on the utility of Lexiscan in other populations and the ability of Lexiscan to increase coronary blood flow in patients with below normal ejection fractions. Additionally further studies may be needed to monitor the effect of Lexiscan in a larger group of patients with renal impairment where the AUC is increased.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The sponsor presents a summary of clinical safety based on the data from 1,651 patients dosed with Lexiscan and a comparative summary of safety data from Lexiscan and adenosine in the two Phase 3 studies (CVT 5131 and CVT 5132). The three safety Sets defined by the sponsor and presented previously in this document will be the basis for safety comparisons.

7.1.1 Deaths

There were a total of 5 deaths of patients participating in the Phase 3 studies. Three of the deaths were in patients who had received adenosine as the randomized psa.
A 48 year old participant in Study CVT 5131 who received Lexiscan died 42 days after the randomized study from complications following surgery for metastatic carcinoid. A 49 year old in the same study who received adenosine died from unknown causes.
In Study CVT 5132 an 86 year old who received Lexiscan died from hemorrhage following cardiac catheterization several days after the randomized study. Other adenosine deaths also appear unrelated to the study.

7.1.2 Other Serious Adverse Events

In Study CVT 5131 there were 10 patients who had serious adverse events. There were several episodes of congestive heart failure or angina occurring at least 48 hours following the randomized scan. Such cardiac events would not be unexpected in the population making up the Phase 3 study. There was also an episode of streptococcal infection 7 days after the randomized study drug. This is an occurrence which is not unexpected in an elderly population.
A similar pattern was noted in Study CVT 5132. There were 5 events that were considered unrelated to the study medication and all resolved by 14-17 days of follow-up. These events included an episode of exacerbation of chronic obstructive pulmonary disease not occurring immediately following the study drug, a coronary occlusion in a known cardiac patient and an episode of gangrene.
Overall, the AE profile of Lexiscan was similar to that of adenosine, the pharmacologic stress agent used as comparator in the two Phase 3 studies. Patients in the Lexiscan group had a numerically lower incidence of some AEs (flushing, chest pain, chest discomfort, and angina pectoris), but a higher incidence of headache. (Table 6) The incidence of dyspnea was similar in the two treatment groups. The duration of these AEs, although in general short (most resolved within 16 minutes after dosing), was slightly longer after Lexiscan. Although some differences in the pattern of AEs in different subgroups were noted (by gender, body weight, or ischemia size category), none were clinically significant. The Lexiscan adverse event profile was not importantly different in patients with renal insufficiency, patients with COPD, and patients with asthma compared to the overall study population.

Only one Serious Adverse Event was attributed to Lexiscan: the exacerbation of an ongoing migraine headache in a patient whose migraine worsened after receiving Lexiscan. AEs considered related to study drug were generally graded as mild and minimal or no treatment was required. Patients receiving Lexiscan had higher HRs that persisted for slightly longer than in adenosine patients. No patient terminated the study prematurely because of an AE related to Lexiscan, but a few patients (≤1%) terminated prematurely because of AEs.
Aminophylline was used to reverse the adverse effects of Lexiscan when deemed appropriate by the investigator; 3% of Lexiscan patients and 2% of adenosine patients received aminophylline in the Phase 3 studies. The AEs for which aminophylline was given in Lexiscan patients (angina, headache, ECG ST segment depression, and chest pain) resolved without further treatment.

7.1.3 Dropouts and Other Significant Adverse Events

A total of 1,451 patients received the initial adenosine dose but did not receive blinded study drug; the majority (n=1100) of these patients were not eligible for randomization because their initial adenosine studies were assessed at the sites as showing 0-1 reversible segments following closure of randomization to patients in this category. Other reasons for not proceeding to randomized dosing are listed below:

7.1.3.1 Overall profile of dropouts

In study CVT 5131 (Patient Nos. 1409-0029 and 1502-0020) were prematurely terminated from the randomized portion of the study due to an AE, IV infiltration. There were no other premature terminations due to an AE in Lexiscan receiving patients.

7.1.3.2 Adverse events associated with dropouts

See section 7.1.3.1 above

7.1.3.3 Other significant adverse events

In the Phase 3 studies (Set 2 safety group), 9% of all patients had AEs requiring any treatment; 9% of Lexiscan patients and 8% of adenosine patients. Following is a review of AEs that required concomitant medications (8% of Lexiscan patients and 6% of adenosine patients).
To reverse AEs investigators had the option to administer aminophylline which acts as an antagonist to adenosine agents. Aminophylline was administered to reverse an AE in 3% (46/1337) of randomized Lexiscan patients and 2% (12/678) of randomized adenosine patients.
For the Set 1 safety group, an additional Lexiscan subject (in Phase 2 study CVT 5122) received aminophylline to reverse AEs, chest pain and headache, experienced approximately 1 minute after administration of open-label Lexiscan. For all Lexiscan patients, the most common AEs for

which aminophylline was given included the following: angina (18/1337), headache (12/1337), ECG ST segment depression (10/1337), and chest pain (7/1337).
Exacerbation of a migraine headache was considered drug-related and reported as a serious AE. The patient received multiple concomitant medications as well as oxygen on the day of study drug dosing.
Of the 1,563 patients who received Lexiscan in Safety Set 1, 47 (3%) experienced a severe AE deemed related to study drug by the study investigator. The most frequently reported (<1%) severe drug-related events included headache, dyspnea, chest discomfort, ECG ST segment depression, palpitations, tachycardia, and dizziness. All but 3 of the events resolved spontaneously or with treatment; 2 headaches and 1 angina pectoris did not resolve during the observation period but were controlled with medication.
In Safety Set 2, those patients who received blinded study drug (n=2,015), severe AEs considered related to study drug were reported in 2% of Lexiscan patients compared to 4% of adenosine patients. Eleven Lexiscan patients reported severe headaches which were described by the investigator as related to study drug, 5 severe dyspneas were study drug-related, and 5 severe ECG ST segment depressions were study drug-related. In the adenosine patients two of the severe, study drug-related AEs were reported at a frequency of 1% (angina pectoris and chest pain) and all others were of a frequency of <1%; 7 patients experienced severe angina pectoris which was described by the investigator as related to study drug, 7 severe chest pains were study drug-related, and 4 severe dyspneas were study drug-related. The 3 events (2 headaches and 1 angina pectoris) described above for Set 1 apply to Set 2 as the patients were from the Phase 3 studies, CVT 5131 and CVT 5132.
Lexiscan patients reported more Gastrointestinal Disorders (Lexiscan 25% vs. adenosine 19%), with a similar proportion (the vast majority) considered drug-related between Lexiscan and adenosine; Lexiscan patients reported less General Disorders and Administration Site Conditions (Lexiscan 28% vs. adenosine 37%) compared to adenosine patients, with a similar proportion drug related; and Lexiscan patients reported less Vascular Disorders (Lexiscan 18% vs. adenosine 28%) compared to adenosine patients, with a similar proportion drug-related. Cardiac Disorders (Lexiscan 17% vs. adenosine 21%) and Respiratory Disorders (Lexiscan 33% vs. adenosine 33%) were reported at a similar frequency for the two study treatment groups.

7.1.4 Other Search Strategies

The FDA requested that the sponsor supply data summaries of rates of common AEs vs. patient weight and no correlation was found (see Appendix II on FDA statistical review)

7.1.5 Common Adverse Events

The common adverse events have been outlined above. Chest discomfort and/or angina pectoris is the most common for both agents. Headaches and dyspnea are additional very commonly seen AEs with both agents.

7.1.5.1 Eliciting adverse events data in the development program

The patients were queried during the procedure about how they were feeling and their impression of the randomized injected agent vs. the initial adenosine injection. The sponsor also contacted each participant with a phone call 24 hours post dosing of the randomized agent and an additional 14-17 day post dosing contact.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

There was a myocardial infarction in a patient in trial 5121(trial of aminophylline reversal of Lexiscan effects) which was severe but felt not to be related to study drug. The investigator attributed the myocardial infarction to the catheterization procedure with dislodgement of a thrombus formed on a guide wire. The remainder of the other AEs in Set 1 map to preferred terms (MEDRA) that are similar to those described for Set 2. The incidence of these events is similar between Set 1 and Set 2, except for the incidence of tachycardia as an AE (which is higher in Set 1 than in Set 2; Set 1 includes studies of higher doses of Lexiscan).
Following administration of blinded study drug, severe AEs considered related to study drug were reported in 2% of Lexiscan patients compared to 4% of adenosine patients. Each of the preferred terms was reported at a frequency of <1% for Lexiscan patients. Eleven Lexiscan patients reported severe headaches which were described by the investigators as related to study drug, 5 severe dyspneas were study drug-related, and 5 severe ECG ST segment depressions were study drug-related.

7.1.5.3 Incidence of common adverse events

See Table 7

7.1.5.4 Common adverse event tables

See Table 7

7.1.5.5 Identifying common and drug-related adverse events

The drug related AEs occurred shortly after receiving the injection so causality appeared obvious.

7.1.5.6 Additional analyses and explorations

Dose dependency was noted in the Phase 2 trial where 400 to 500 mcg were compared. The incidence of tachycardia was much higher in the 500 mcg group and hence 400 mcg became the standard dose for the Phase 3 trials.
Since the overwhelming number of patients in the Phase 3 trials were elderly, Caucasian males no demographic interactions could be explored.

7.1.6 Less Common Adverse Events

The Adverse Event noted as a rare event was the exacerbation of a migraine headache.

7.1.7 Laboratory Findings

There were no abnormal laboratory findings. Patients with laboratory abnormalities upon entering the study had no alternation to those abnormalities as a result of participation.

7.1.7.1 Overview of laboratory testing in the development program

7.1.7.2 Laboratory testing included standard hematology, clinical chemistry measurements and ECGs.

There are no long term data available to evaluate late occurring laboratory abnormalities. However no such abnormalities are expected.

7.1.7.3 Standard analyses and explorations of laboratory data

The Phase 3 studies included the obtaining of laboratory tests on all the participants. As noted above no safety signals were noted.
Although many patients in Set 2 had out of range laboratory values, they were often present prior to starting the study, or were not unexpected given the age, obesity, medical histories, and general state of health of patients referred for stress testing. Given that these were single-dose studies, the short duration of the study and timing of the termination laboratory testing within 1-2hrs of dosing; it was not surprising that no drug-related, clinically significant changes in clinical laboratory values were noted. However, an increase in glucose values as well as a clinically insignificant increase in neutrophils was noted at termination.
Between baseline and termination, glucose values increased for both adenosine and Lexiscan patients. Median glucose values were 5.40 mmol/L (range 1.94 to 26.76 mmol/L) at baseline for Lexiscan patients and 5.33 mmol/L (range 1.94 to 26.76 mmol/L) for adenosine patients. At termination, median glucose was 6.66 mmol/L (range 0.10 to 40.97 mmol/L) for Lexiscan patients and 6.72 mmol/L (range 0.98 to 28.98 mmol/L) for adenosine patients. A third (33%) of the patients in Set 2 had diabetes, and 22% had abnormal baseline glucose values. Similar percentages of patients in the Lexiscan and adenosine groups had diabetes. Diabetics, whether they received Lexiscan or adenosine, were more likely to have an elevated glucose at termination than non-diabetics.
The increase in glucose at termination was not considered clinically significant and could be a consequence of the conduct of the study. Although not specified by the protocol, many study sites required that patients fast before receiving the pharmacologic stress agent. Baseline blood

samples drawn before dosing would therefore be fasting samples. Following the randomized scan, but before the termination procedures (which included collection of blood samples for laboratory testing) patients were allowed to eat: the termination laboratory results were probably postprandial samples. In addition, the protocol did not restrict the use of hypoglycemic agents on the day of dosing.
The mean white blood cell (WBC) count and the percentage neutrophils increased slightly more at termination for Lexiscan patients. The mean WBC count at study termination was 7.67±2.23 x 10^9/L for Lexiscan patients (baseline: 6.90±2.03 x10^9/L) and 7.20±1.99 x 10^9/L (baseline: 6.77±1.91 x 10^9/L) for adenosine patients. The mean neutrophil value at study termination was 67±19.5% for Lexiscan patients and 63±10.1% for adenosine patients. The small increase in WBC count and neutrophil percentage were not considered clinically significant. The sponsor speculates that the small increase in WBC count may be due to decreased adhesion of neutrophils to the endothelium (demargination), facilitated by activation of A2A-AdoR.
Laboratory abnormalities were reported as AEs infrequently (<1% of patients), and similar abnormalities were reported by patients receiving Lexiscan and by those receiving adenosine. Thirteen patients who received Lexiscan had at least one laboratory abnormality as an AE considered possibly or probably related to the study drug: 7 patients had AEs related to hematology values, and 6 patients had AEs related to clinical chemistry results.

7.1.7.3.1 Analyses focused on measures of central tendency
No safety signals were identified.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal
No clinically important shifts were observed.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities
No marked outliers or drop outs were observed.

7.1.7.4 Additional analyses and explorations

No safety signals observed

7.1.8 Vital Signs

Vital signs have been discussed in earlier sections. The major change following Lexiscan was tachycardia which did not induce serious reactions in study patients.

7.1.8.1 Overview of vital signs testing in the development program

Vital Signs were obtained uniformly during the performance of the two identical Phase 3 trials. Blood pressure and heart rate were to be measured at the following time points: (Table 8)

- Within 48 hours prior to the initial adenosine scan (referred to as Baseline 1).

- Within 10 minutes prior to dosing with the randomized stress agent (two measurements) and at 2, 4, 6, 8, 10, 12, 14, 16, 30 and 45 minutes after the start of the 6 minute infusion. Vital signs measurements were to be obtained from the bolus limb for the randomized scan.
- At study termination.
- If a patient developed a clinically significant change from his or her Baseline 1 vital signs, repeat measurements were to be recorded as clinically indicated until resolution.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

The obtained vital signs were analyzed using descriptive statistics.

7.1.8.3 Standard analyses and explorations of vital signs data

After the start of the blinded infusion, heart rate (HR) increases for Lexiscan patients were higher and sustained slightly longer than HR for adenosine patients.
The time of peak HR and the greatest mean change in HR occurred at nominal time 4 minutes after the start of the blinded infusion (1.5 minutes after the blinded bolus); the first time point at which both treatment groups had received active drug. For the Lexiscan patients, the mean HR was 87±15.7 bpm (with a median of 87 bpm and 25^{th}-75^{th} percentile 76-98 bpm) and the greatest mean increase in HR was 21±11.9 bpm (median of 21 bpm and 25^{th}-75^{th} percentile 14-29 bpm). For adenosine patients, the mean HR was 81±14.8 bpm (median of 80 bpm and 25^{th}-75^{th} percentile 71-90 bpm) and the greatest mean increase in HR was 15±11.3 bpm (measured at both nominal time 4 minutes [median of 15 bpm and 25^{th}-75^{th} percentile 8-21 bpm] and 6 minutes [median of 15 bpm and 25^{th}-75^{th} percentile 8-22 bpm] after the start of the blinded infusion. The maximum HR recorded for any Lexiscan patient was 142 bpm occurring at 4 minutes post start of the blinded infusion, and for any adenosine patient was 164 bpm occurring at 10 minutes post start of the blinded infusion. The mean HR returned to within 10 bpm of baseline by 10 minutes for Lexiscan patients, by 8 minutes for adenosine patients. HR increased by >50 bpm with a similar incidence in the two groups: 1.5% of Lexiscan patients versus 1.2% of adenosine patients. More modest HR increases were most frequently among Lexiscan patients than adenosine patients. Most of the patients with HR>100 bpm after dosing with either Lexiscan (22.2%) or adenosine (13.0%) had HR <100 bpm at baseline (21.3% for Lexiscan patients vs. 12.4% for adenosine patients), although the single adenosine patient with HR> 140 bpm had HR> 140 bpm at baseline. None of the patients with HR> 140 bpm had this recorded on a study specified ECG.
Analyses of the maximum HR and maximum increase in HR for each patient were done for the first 16 minutes and for the first 45 minutes after the start of the blinded infusion. Nearly all maxima occurred in the first 16 minutes for both Lexiscan and adenosine. For Lexiscan patients, the mean maximum HR was 89±15.0 bpm (range 48-142 bpm) and mean maximum increase in HR was 23±11.0 bpm (range -20 to +70 bpm). For adenosine patients, the mean maximum HR was 85±14.6 bpm (range: 46-165 bpm) and the mean maximum increase in HR was 19±10.6 bpm (range -16 to +64 bpm).

AEs associated with changes in HR were reported with approximately the same frequency in Lexiscan and adenosine patients. The ECG changes will be discussed separately. Palpitations were reported by 3% of patients in each group (39 Lexiscan and 17 adenosine patients), HR increased by <1% of patients in each group (8 Lexiscan patients and 3 adenosine patients), and an abnormal pulse was reported by 1 Lexiscan patient and no adenosine patients.

Blood Pressure Changes
Following the start of the randomized infusion, there was a slight decrease in systolic blood pressure which was similar for patients given Lexiscan and patients given adenosine. The mean systolic blood pressure for Lexiscan patients declined from 137±21.0 mm Hg (range: 84-217 mm Hg) to 135±22.7 mm Hg (range: 75-210 mm Hg) at 4 minutes after the start of the blinded infusion (1.5 minutes after the blinded bolus) and was essentially unchanged through termination; the systolic blood pressure for adenosine patients declined from 136±20.2 mm Hg (range: 88-216 mm Hg) to 129±21.8 mm Hg (range: 74-212 mm Hg) at 6 minutes after the start of the blinded infusion and rose thereafter to 135±21.1 mm Hg (range: 82-207 mm Hg) at 14 minutes after the start of the blinded infusion.
Diastolic blood pressure also showed a slight decrease following the start of the randomized infusion that was similar for patients given either Lexiscan or adenosine. The lowest mean diastolic blood pressure occurred at 4 minutes after the start of the randomized infusion and was 74±12.3 mm Hg (range: 40-120 mm Hg) for Lexiscan patients, and occurred at 6 minutes after the start of the randomized infusion and was 72±12.6 mm Hg (range: 36-119 mm Hg) for adenosine patients. The greatest mean decrease from baseline was 4 mm Hg at 4 minutes and 6 mm Hg at 6 minutes after the start of the randomized infusion for Lexiscan and adenosine patients, respectively.

7.1.8.3.1 Analyses focused on measures of central tendencies
See discussion above.

7.1.9 Electrocardiograms (ECGs)

A 12 lead ECG was obtained at the following time points:

- Within 48 hours prior to the initial adenosine scan (Baseline 1).
- For the randomized scan, at pre-dose and at 4, 6,8, 10, 16, 30 and 45 minutes after the start of the 6 minute infusion.
- At study termination.
- If a patient developed a clinically significant ECG change from his or her Baseline 1 ECG, repeat tracings were to be obtained, as clinically indicated.

ECGs were to be acquired digitally, however, standard ECG monitoring could have been performed simultaneously using electrode patches provided by the ECG core laboratory that enabled dual monitoring. ECGs were to be printed, reviewed, signed, and dated by the investigator. The original digital ECGs were sent to the ECG core laboratory electronically for analysis and inclusion in the database. The paper tracings were to be kept at the investigative site.

The major ECG change was the development of ST segment depression – not unexpected since the purpose of the pharmacologic stress agent was to induce ischemia and hence its ECG manifestation, ST segment depression. (Table 8)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

ECGs were obtained throughout the Lexiscan development program. As mentioned earlier, based on the Phase 2 studies no significant effect was found on the QT interval. After correcting the QT interval for HR, an apparent, transient QTcF interval prolongation was seen in Lexiscan patients at nominal time 4 minutes after the start of the blinded infusion (1.5 min after the blinded bolus), with a mean QTcF prolongation of 12±20.7 msec (range -68 to 127 msec). The QTcF interval prolongation was less pronounced with adenosine (mean maximum change of 6±18.9 msec [range -78 to 164 msec]).
Only 1 Lexiscan patient, Patient No. 2806-2067 in CVT 5131, reported an AE of QT prolongation. On a study-specified ECG, the QTcF was 419.88 msec at baseline and 457.45 msec at 4 minutes after the start of the blinded infusion, the time at which the AE began. The QTcF decreased thereafter. Somatic tremor was noted as well.
Preclinical studies show no direct effect of Lexiscan on left ventricular repolarization; increases in HR due to Lexiscan occur through sympathetic stimulation. In CVT 5111, no transient increase in QTc and no QTc hysteresis was observed using the study-derived correction formula to calculate QTc optimized from pooled placebo data. The prolongation of QTcF at 4 minutes can be explained by a slower adaptation of the QT interval to the rapid change in HR (hysteresis), thus causing an artificial QTc increase.
The types of treatment-emergent ECG changes were not unexpected and the incidence of these findings (rhythm abnormalities, PACs, PVCs, AV conduction abnormalities [other than AV blocks], ventricular conduction abnormalities, ischemic ST segment changes, and T wave abnormalities) was similar after dosing with Lexiscan and after adenosine. First and 2nd degree AV block are less frequent with Lexiscan than with adenosine.
The treatment-emergent ECG changes were generally identified within the first 16 minutes after dosing, the time of most frequent ECG recordings, for both Lexiscan and adenosine patients. The incidence of new or continuing findings generally decreased thereafter. ECG findings of PVCs, ischemic ST segment changes, and T wave abnormalities were slightly more prevalent in Lexiscan patients than in adenosine patients at later time points (after 16 minutes postdose but before discharge, and at discharge).
None of the patients on Lexiscan and 1 patient on adenosine showed a treatment-emergent ventricular arrhythmia on study-specific ECGs. Ventricular arrhythmia was reported as an AE for 2 patients: at 28 minutes after dosing for a few seconds for 1 patient on Lexiscan (Patient No. 2809-1392 in CVT 5131) considered not drug-related, and at 7 minutes after the start of the infusion for 1 patient on adenosine (Patient No. 2810-0947 in CVT 5132) considered drug-related.
The reported incidence of AV block (either reported as an AE or on a study-specified ECG) in randomized adenosine patients in Set 2 is low compared to data reported in the Adenoscan (adenosine) Injection package insert (2.6% 2nd degree AV block and 0.8% 3rd degree AV block). Patients with 2nd or 3rd degree AV block were excluded from the Phase 3 trials because the

adenosine comparator was contraindicated in these patients. However, 76 Lexiscan patients (6.3%) and 38 adenosine patients (6.1%) had 1st degree AV block on the study-specified ECG both at baseline and after randomized dosing, and 1 Lexiscan patient and 1 adenosine patient had 2nd degree AV block on the study-specified ECG both at baseline and after randomized dosing. Treatment-emergent 1st degree AV block was noted on study-specified ECGs for 34 (2.8%) Lexiscan patients and 43 (7.0%) adenosine patients. First-degree AV block was reported as an AE in 2 Lexiscan patients and in 4 adenosine patients. Two of these patients, had 1st degree AV block after both the initial and the randomized doses.
Treatment-emergent 2nd degree AV block was noted on study-specified ECGs for 1 (0.1%) Lexiscan patient and 9 (1.5%) adenosine patients. An AE of 2nd degree AV block was reported for 2 Lexiscan patients (patient nos. 1502-0063 and 2806-1428 both in CVT 5131) and 3 adenosine patients. For Lexiscan Patient No. 1502-0063, the 2nd degree AV block occurred after the start of the blinded infusion but before the bolus was given, and therefore was not Lexiscan treatment-emergent. For Lexiscan Patient No. 2806-1428, the study-specified ECG at 6 minutes after the start of the blinded infusion (3.5 minutes after the blinded bolus) showed a single dropped beat. The baseline and other on-treatment ECGs showed 1st degree AV block. For the 9 adenosine patients with 2nd degree AV block on study-specified ECGs, the mean number of non-conducted beats during the episode of 2nd degree AV block was 2.1 (range 1-5). No episodes of AV block after randomized dosing required intervention. These clinical data are consistent with the preclinical finding that Lexiscan has enhanced A2A-AdoR selectivity compared with adenosine with less effect on A_1 receptor-mediated AV node conduction.
None of the patients on either Lexiscan or adenosine had evidence of 3rd degree AV block noted on study-specified ECGs. One Lexiscan patient had a treatment-emergent AV conduction abnormality other than AV block on a study-specified ECG.
Treatment-emergent ischemic ST segment changes were identified on study-specified ECGs in 17.6% of Lexiscan patients and in 21.8% of adenosine patients at any time post dose. A small percentage of patients had ischemic ST segment changes both at baseline and post dose (5.1% of Lexiscan patients vs. 4.4% of adenosine patients). At discharge, 5.1% of Lexiscan patients and 2.9% of adenosine patients had treatment-emergent ischemic ST segment changes identified on study-specified ECGs.
ECG changes reported as AEs include ST segment depression (reported in 67 [5%] Lexiscan and in 45 [7%] adenosine patients) and, as reported in <1% of Lexiscan patients: ECG T wave abnormal, ECG signs of myocardial ischemia, ECG ST-T change, ECG ST segment abnormal, ST segment elevation, ECG ST-T segment depression. No AE or MI was reported in these patients.

ECGs were read by the site investigators.

7.1.10 Immunogenicity

Immunogenicity studies were not required for this chemical entity.

7.1.11 Human Carcinogenicity

No data are available and none are necessary.

7.1.12 Special Safety Studies

As noted earlier, Lexiscan has no effect on the QT interval. The transient prolongation of QT interval with the onset of Lexiscan induced tachycardia was considered to be QT hysteresis. QT hysteresis is the phenomenon of a lag in QT interval shortening as other sections of ECG QRS complex decrease with increasing heart rate. Hence the QT interval appears prolonged relative to the increasing heart rate. QT hysteresis is innocuous.
The concerns for the induction of higher orders of AV block by Lexiscan were monitored through the frequent ECGs.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There are no withdrawal phenomena and/or abuse potential for this chemical entity

7.1.14 Human Reproduction and Pregnancy Data

No information is available of the effect of Lexiscan on human reproduction or pregnancy and no human studies are needed.

7.1.15 Assessment of Effect on Growth

No information available and none is needed

7.1.16 Overdose Experience

Study CVT 5111, a dose finding trial, evaluated higher doses of Lexiscan than the dose chosen for the Phase 3 studies. In the supine phase, AEs were more prevalent at Lexiscan doses of $\geq$3.0 mcg/kg. Overall, 50% of subjects (healthy males) dosed in the supine phase experienced an adverse event involving the cardiovascular system, with vasodilatation, palpitation and T-wave inversion as the more commonly reported events. Other frequently reported events involved the body as a whole and included headaches and asthenia.
In the standing position, more subjects reported adverse events at the lower dose of Lexiscan (starting at 0.1mcg/kg) compared to the supine phase. Overall, in the standing phase 54% of subjects experienced an adverse event involving the cardiovascular system, with palpitations, pallor, and T-wave inversion as the more frequently reported cardiovascular events. The nervous system had the next most frequently reported adverse events with 41% of subjects experiencing dizziness. In the standing position, subjects were not dosed at the 30.0 mcg/kg because intolerable adverse events were reported at the 20.0 mcg/kg dose, thus halting dose escalation.

7.1.17 Postmarketing Experience

No postmarketing information is available.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The safety databases were described in section 4.

7.2.1.1 Study type and design/patient enumeration

Specific safety issues that were addressed in the Phase 2 clinical trials were: safety in COPD and in renal insufficiency. Please see earlier Tables of Clinical Studies. (Section 4.2)

7.2.1.2 Demographics

The study population is generally consistent with the population affected by CAD.

7.2.1.3 Extent of exposure (dose/duration)

This is a diagnostic agent for primarily for single use.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

There are no other secondary sources of information.

7.2.2.1 Postmarketing experience

There is no postmarketing experience.

7.2.2.2 Literature

The sponsor presents numerous citations which deal with: the process of nuclear stress testing; evaluation of the various nuclear isotope protocols ; and papers documenting the development and clinical testing of Lexiscan. No new data or trials that were not part of the NDA application were presented.

7.2.3 Adequacy of Overall Clinical Experience

Lexiscan has been adequately tested to assess safety for its intended use. Over 1700 patients received the medication – except for 1 dosing study – the patients received the 400 mcg, the dose intended for clinical use. This dose and duration of exposure was adequate to assess safety for the intended use. The class effect of adenosine type agents causing AV block was appropriately studied through repetitive ECGs. Lexiscan had less of an incidence of AV block than, adenosine the comparator. Patients in the Phase 3 trials were representative of individuals who might receive this medication; older males with concomitant chronic conditions. Patients with COPD were excluded from the large Phase 3 studies. This exclusion does not permit an evaluation of Lexiscan in the patient group where it might find clinical use – COPD patients in whom the treating physician is reticent to use adenosine for fear of its bronchospastic effects.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

See FDA's toxicology-pharmacology review.

7.2.5 Adequacy of Routine Clinical Testing

The routine clinical testing for this NDA is adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Several Phase 1 studies elucidated the metabolic pathway and provided information suggesting Lexiscan would be safe in patients with impaired liver or kidney function. Further information is provided by the FDA Pharmacology-Toxicology reviewer.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

As noted in previous sections, the sponsor has extensively researched the possibility of Lexiscan prolonging the QT interval. No significant prolongation was found.

7.2.8 Assessment of Quality and Completeness of Data

The sponsor has provided adequate data to assess the safety and efficacy of Lexiscan. The performance of Lexiscan in all the ischemia groups supports the efficacy claims.

7.2.9 Additional Submissions, Including Safety Update

On September 14, 2007 the sponsor provided an update where the small studies of COPD patients and patients who underwent exercise were included. No major new safety findings were noted after inclusion of these new data. Table 9, Table 10 presenting ECG abnormalities contain data reflecting the safety date and the changes are highlighted.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Migraine Headache Exacerbation
This AE occurred in a patient receiving Lexiscan. This AE occurred in a patient with a history of migraines who may have already been experiencing a migraine prior to the inception of the testing procedure. Migraine being such a variable occurrence and initiated by a multiplicity of factors, makes further analysis of the AE problematic.

Chest Pain
By design, the Phase 3 studies were performed in patients prone to chest pain due to underlying cardiovascular disorders. Additionally, chest pain is a ubiquitous finding in the middle aged population, as manifested by the numerous emergency room visits for this disorder. Hence, this AE is to be expected and its specific cause difficult to find.

Dyspnea
Shortness of breath – Dyspnea- without a measured decrease in oxygenation is a symptom without a concomitant sign. The sensation of dyspnea may also be a displaced sensation of tachycardia. This AE therefore is not a major concern for the reviewer.

7.4 General Methodology

There are no further methodology issues to discuss.

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

As mentioned earlier, results from the two Phase 3 trials, CVT 5131 and CVT 5132 were initially presented individually and then in a combined form. The two trials yielded virtually identical results and hence pooling of the efficacy and safety results is justified. Additionally the sponsor

developed the safety sets 1, 2, 3 which is an appropriate method to categorize the various groups participating in the trials, particularly from a safety viewpoint.

7.4.1.2 Combining data

Pooling of data as noted above.

7.4.2 Explorations for Predictive Factors

No common predictive factors have been found.

7.4.2.1 Explorations for dose dependency for adverse findings

This exploration was discussed previously with a Phase 2 trial performed to chose the 400mcg dose for the Phase 3 studies.

7.4.2.2 Explorations for time dependency for adverse findings

Patients were followed up several days following the Phase 3 studies to query them for any late occurring AEs. None were observed.

7.4.2.3 Explorations for drug-demographic interactions

No significant interactions were noted.

7.4.2.4 Explorations for drug-disease interactions

No significant interactions were noted.

7.4.2.5 Explorations for drug-drug interactions

No significant interactions were noted.

7.4.3 Causality Determination

Lexiscan exists for a short time within the circulation. AEs that occurred such as dyspnea and tachycardia were expected and occurred within several minutes of receiving Lexiscan. There were no delayed AEs.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The chosen dose of 400 mcg as outlined earlier in this review functioned as well as adenosine as a pharmacologic stress agent. No unanticipated AEs were evident. In the Phase 1 and Phase 2 studies the 500 mcg dose was associated with a higher incidence of tachycardia with no added imaging advantage. Clinically no increase in AEs was noted in the renal insufficiency patients, despite Lexiscan having a prolonged clearance in that group. In patients with obstructive lung disease, asthma and COPD, Lexiscan did not induce a significant increase in bronchospastic symptoms requiring treatment.
Similarly Lexiscan was given to less than 100 patients with obstructive lung disease.
Obstructive lung disease patients were excluded from the Phase 3 trial because adenosine was a comparator with a labeling warning about use in this group of patients. An observational study of Lexiscan use in obstructive lung disease patients should be considered.

Drug-Drug Interactions
There are no interactions.

8.2 Special Populations

There are no effects of hepatic dysfunction on the metabolism of Lexiscan. Patient groups possibly requiring special consideration are mentioned in section 8.1.

8.3 Pediatrics

A pediatric waiver was granted because there is no need for this diagnostic drug in children.

8.4 Advisory Committee Meeting

A meeting was not needed.

8.5 Literature Review

The literature did not contribute any important safety or efficacy data.

8.6 Postmarketing Risk Management Plan

No postmarketing risk management plan has been submitted.

9 OVERALL ASSESSMENT

9.1 Conclusions

Lexiscan functions as well as adenosine as a pharmacologic stress agent. Though many of the AEs associated with Lexiscan are similar in number to adenosine, most importantly Lexiscan has less of an incidence of second degree (or high degree) heart block.

9.2 Recommendation on Regulatory Action

Lexiscan should be approved as pharmacologic stress agent. Compared to the existing, licensed agent, adenosine, Lexiscan has less risk for the development of second degree or higher heart block. Lexiscan did have a pattern of non cardiac AEs that was similar to adenosine. However, these AEs were of a transient, relatively mild nature. Lexiscan did cause an increased incidence of headaches. These headaches, though more prominent than with adenosine, were of self-limited with no prolonged sequealae. Though not explicitly demonstrated in the Phase 3 trials, given the receptor selectively of Lexiscan, this agent should have less of a deleterious effect than adenosine on bronchospastic pulmonary patients. Theoretical concerns have been raised about the prolonged metabolism of Lexiscan in patients with renal insufficiency. However no increased incidence of AEs was found in this patient group.

9.3 Recommendation on Postmarketing Actions

This reviewer has proposed a Phase 4 studies to further evaluate the safety of Lexiscan in patients with obstructive lung disease, including asthma and chronic obstructive lung disease. In the older age group where Lexiscan would find the most use, in many clinical cases differentiating between asthma and chronic obstructive lung disease is difficult.
The sponsor is requested to develop a Phase 4 protocol to further assess safety of Lexiscan in patients with obstructive lung disease (both asthma and chronic obstructive lung disease).

9.3.1 Risk Management Activity

At the time of this document's completion, the risk management program has not been finalized.

9.4 Comments to Applicant

We have the following clinical comments:

1. You have provided minimal data on the effects of Lexiscan on patients with diminished left ventricular ejection fraction. We request that in your periodic safety updates you provide a summary of all spontaneous adverse event reports and of any literature reports (e.g. hemodynamic studies) in this patient population.

10 APPENDICES

10.1 Line-by-Line Labeling Review

The reviewer recommends that information on risks, of myocardial ischemia, AV block, hypotension and bronchospasm be made more prominent in the package insert.

11 APPENDIX I – TABLES AND FIGURES

Figure 1: Dosing Scheme for Phase 3 Studies

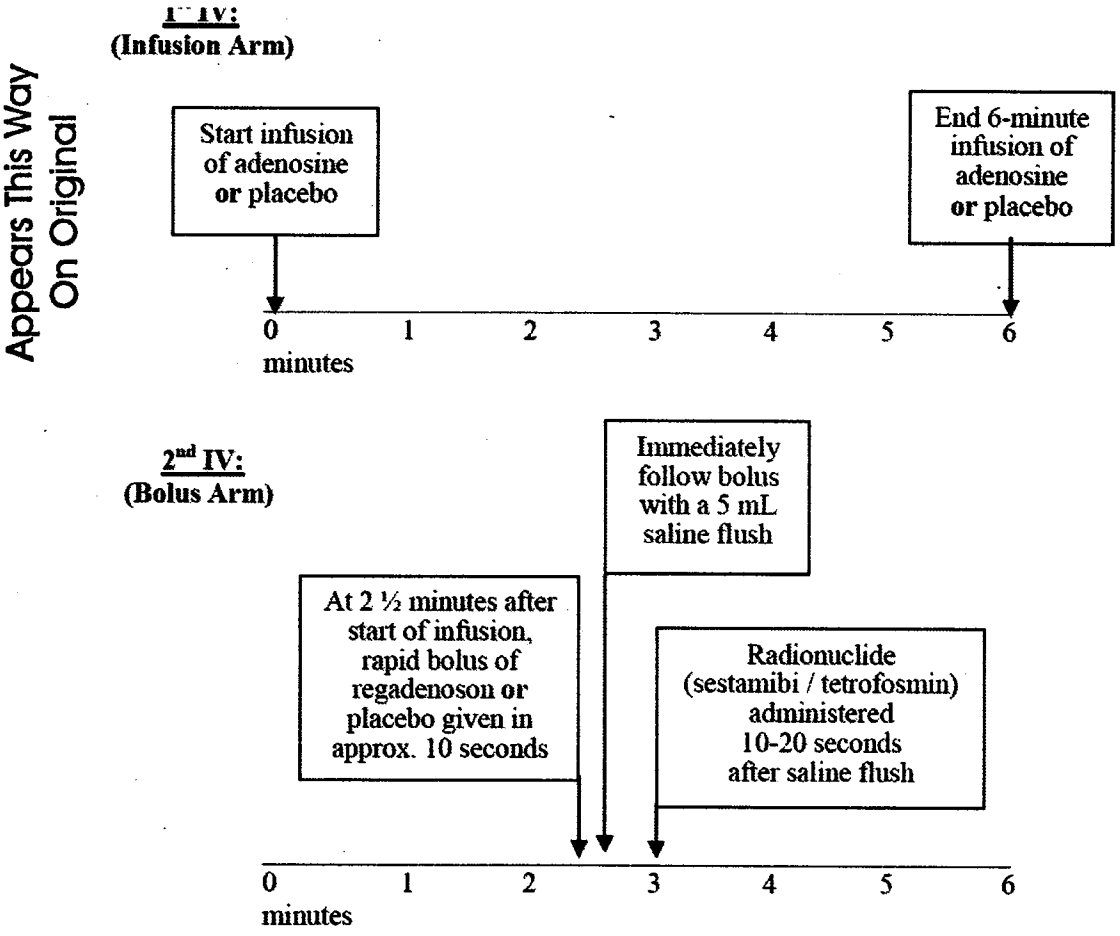

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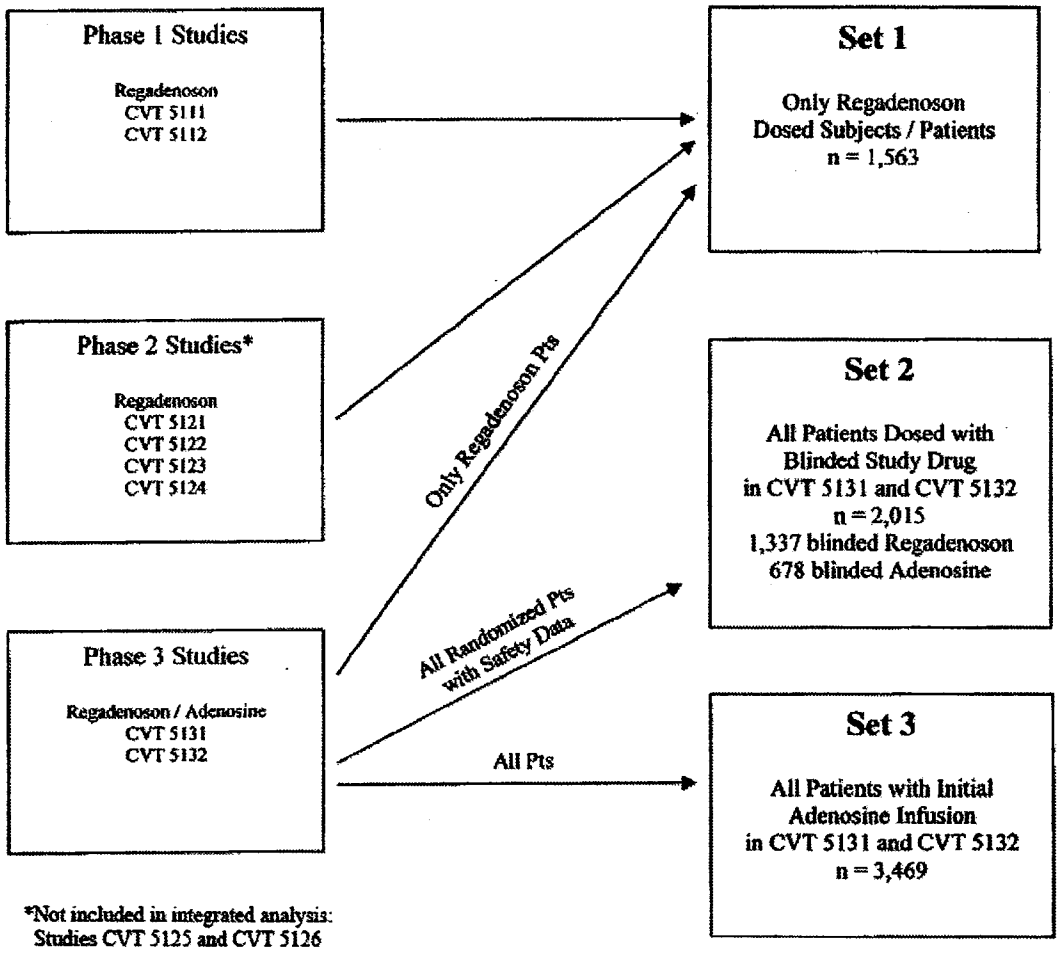
Table 1: Sequence of Phase 3 Study Design

Evaluation	Clinical Encounter 1 Screening within 30 days prior to initial scan	Clinical Encounter 2 Baseline 1 within 48 hrs prior to initial adenosine scan	Clinical Encounter 3 Initial adenosine scan rest & stress	Clinical Encounter 4 Follow-up contact day after initial stress scan	Clinical Encounter 5 Baseline 2 immediately prior to randomized stress scan	Clinical Encounter 6 Randomized scan (24 hours-60 days post initial scan)	Clinical Encounter 7 Termination 1-2 hours post randomized scan	Clinical Encounter 8 Follow-up contact day after randomized scan	Clinical Encounter 9 Safety call 14-17 days post randomized scan	Clinical Encounter 10 Angiography data collection 12 weeks post randomized scan
Informed Consent	X									
HIPAA (US sites only)	X									
Inclusion/Exclusion Criteria	X				X					
Cardiac and Medical Hx		X[12]								
Medication Hx/Con Meds		X	X		X	X	X	X		
Physical Examination		X[12]			X[8]		X			
Height[1] and Weight		X			X					
Vital Signs[2]		X				X[3]	X			
12-lead ECG		X				X[7]	X			
Safety Labs		X			X		X			
Caffeine & Theophylline Samples			X			X				
Pharmacokinetics						X[6]	X[7]			
Serum βHCG or urine pregnancy test		X[4]			X[4]					
Qualifying Criteria					X					
Verbal Assessment questionnaire						X[5]				
Adverse Events		X	X[11]	X	X	X[11]	X	X	X	
Image Analysis Score			X			X				
Angiogram Report										X[10]

[1] Height only obtained once at Baseline 1
[2] Blood pressure and heart rate
[3] Obtain 2 BPs at pre-dose (within 10 minutes prior to dosing) and at 2, 4, 6, 8, 10, 12, 14, 16, 30 and 45 minutes after the start of the 6-minute infusion
[4] Serum βHCG or urine pregnancy test must be performed at the local laboratory within 24 hours of dosing and must be confirmed negative
[5] Questionnaire administered verbally at 30 minutes after the start of the 6-minute infusion
[6] PKs drawn 7-12 min after start of 6-min infusion, 20-30 min after start of 6-min infusion, and 45-60 min after start of 6-min infusion
[7] PK drawn at study termination and again if possible (for in-patient), 4-6 hours post dose
[8] Partial physical exam only for Baseline 2
[9] Obtain pre-dose and at 4, 6, 8, 10, 16, 30 and 45 minutes after the start of the 6-minute infusion
[10] Collect angiogram reports done anytime between 12 weeks prior and 12 weeks post randomized scan
[11] Adverse events will be indirectly solicited at 8, 15, and 30 minutes following the start of the infusion for both the initial and randomized studies.
[12] The Investigator's assessment of the patient's chest pain characteristics in the previous 3 months should occur at baseline.

Figure 2: Safety Analysis Groups



*Not included in integrated analysis: Studies CVT 5125 and CVT 5126

Table 2: Patients Terminating Prematurely

	No. of Patients
No. Terminating prematurely before blinded study medication	1451
Primary reason	
Assessed as having 0–1 reversible defects after the study was closed to patients in this category	1100
Failed to meet other additional qualifying criteria	35
Adverse event	49
Inappropriate enrollment	5
Noncompliance	26
Elective withdrawal	149
Lost to follow-up	13
Death	1
Other	72

Table 3: Comparison of Ischemic Segments Source for Calculation of Primary Efficacy Results for Study CVT#5131

(Parentheticals are % of Total Sample)
(AI = Initial Adenosine ; AR = Randomized Adenosine RR = Randomized Regadenoson)

	Adenosine-Adenosine			
	AR= 1	AR= 2	AR= 3	Marginals
AI = 1	218 (59%)	34 (9%)	3 (1%)	255 (69%)
AI = 2	24 (6%)	47 (13%)	13 (3%)	84 (22%)
AI = 3	7 (2%)	12 (3%)	14 (4%)	33 (9%)
Marginals	249 (67%)	93 (25%)	30 (8%)	372

	Adenosine-Regadenoson			
	RR = 1	RR = 2	RR = 3	Marginals
AI = 1	436 (59%)	64 (9%)	5 (1%)	505 (68%)
AI = 2	55 (7%)	94 (13%)	23 (3%)	172 (23%)
AI = 3	8 (1%)	27 (4%)	29 (9%)	64 (9%)
Marginals	499 (67%)	185 (25%)	57 (8%)	741

The Agreement Scores derived from these tables, along with their difference, and the 95% CI for the difference follow:

A^*_C = Adenosine - Adenosine Agreement = .61

A^*_T = Adenosine – Regadenoson Agreement = .62 ;

$D^* = A^*_T - A^*_C$ = Difference = .01

95% Two-sided CI for D^* = (-.07 , +.09)

Note then that: Lower Limit for the 95% Two-sided CI for D^* = - .07

The Sponsor set the non-Inferiority boundary at -.133

The conclusion is Non-Inferiority.

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Table 4: Source Table For Primary Efficacy Results for Study CVT#5132

	Adenosine-Adenosine			
	AR= 1	AR= 2	AR= 3	Marginals
AI = 1	144 (56%)	20 (8%)	11 (4%)	175 (68%)
AI = 2	22 (8%)	31 (12%)	10 (4%)	63 (24%)
AI = 3	4 (1%)	4 (1%)	13 (5%)	21 (8%)
Marginals	170 (66%)	55 (21%)	34 (13%)	259

	Adenosine-Regadenoson			
	RR = 1	RR = 2	RR = 3	Marginals
AI = 1	270 (54%)	45 (9%)	14 (3%)	329 (66%)
AI = 2	46 (9%)	50 (10%)	26 (5%)	122 (24%)
AI = 3	5 (1%)	11 (2%)	32 (6%)	48 (10%)
Marginals	321 (64%)	106 (22%)	72 (14%)	499

The Agreement Scores derived from these tables, along with their difference, and the 95% CI for the difference follow:

A^*_C = Adenosine-Adenosine Agreement = .64

A^*_T = Adenosine – Regadenoson Agreement = .63

$D^* = A^*_T - A^*_C$ = Difference = - .01 ;

95% Two-sided CI for D^* = (-.11 , +.09)

Note then that: Lower Limit for the 95% Two-sided CI for D^* = - .11

The Sponsor set the non-Inferiority boundary at -.133

The conclusion is Non-Inferiority.

Table 5: Agreement Rates Between Scans

	CVT 5131	CVT 5132	Both Trials
Adenosine – Adenosine Agreement Rate (± SE)	61 ± 3%	64 ± 4%	62 ± 3%
Adenosine – Lexiscan Agreement Rate (± SE)	62 ± 2%	63 ± 3%	63 ± 2%
Rate Difference (Lexiscan – Adenosine) (± SE)	1 ± 4%	-1 ± 5%	0± 3%
95% Confidence Interval	-7.5, 9.2%	-11.2, 8.7%	-6.2, 6.8%

Table 6: Common Adverse Events Combined Phase 3 Trials (CVT 5132 and CVT 5131)

Adverse Event	Lexiscan (%)	Adenosine (%)
Dyspnea	28	26
Headache	26 24 (CVT 5131) 29 (CVT5132)	17
Chest discomfort	13	18
Angina	10	15

Table 7: Adverse Events (AE) By Age and System Organ Class

System Organ Class Preferred Term	Adenosine (Age)				Lexiscan (Age)			
	18-64 (n=310)	65-74 (n=223)	75 and over (n=145)	All (n=678)	18-64 (n=582)	65-74 (n=434)	75 and over (n=321)	All (n=1337)
CARDIAC DISORDERS								
ANGINA PECTORIS	53 (17%)	31 (14%)	15 (10%)	99 (15%)	65 (11%))	42 (10%)	23 (7%)	130 (10%)
GASTROINTESTINAL DISORDERS								
NAUSEA	20 (6%)	14 (6%)	8 (6%)	42 (6%)	39 (7%)	29 (7%)	18 (6%)	86 (6%)
ABDOMINAL DISCOMFORT	6 (2%)	6 (3%)	2 (1%)	14 (2%)	26 (4%)	25 (6%)	19 (6%)	70 (5%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS								
CHEST DISCOMFORT	52 (17%)	30 13%)	37 (26%)	119 (18%)	79 (14%)	41 (9%)	48 (15%)	168 (13%)
CHEST PAIN	29 (9%)	24 (11%)	16 (11%)	69 (10%)	44 (8%)	26 (6%)	26 (8%)	96 (7%)
FEELING HOT	21 (7%)	19 (9%)	14 (10%)	54 (8%)	33 (6%)	22 (5%)	15 (5%)	70 (5%)
INVESTIGATIONS								
ELECTROCARDIOGRAM ST SEGMENT DEPRESSION	20 (6%)	18 (8%)	7 (5%)	45 (7%)	26 (4%)	26 (6%)	15 (5%)	67 (5%)
NERVOUS SYSTEM DISORDERS								
HEADACHE	53 (17%)	32 (14%)	28 (19%)	113 (17%)	164 (28%)	96 (22%)	82 (26%)	342 (26%)
DIZZINESS	23 (7%)	12 (5%)	11 (8%)	46 (7%)	54 (9%)	28 (6%)	24 (7%)	106 (8%)
DYSGEUSIA	21 (7%)	14 (6%)	10 (7%)	45 (7%)	35 (6%)	24 (6%)	12 (4%)	71 (5%)
RESPIRATORY, THORACIC AND MEDIASTINALDISORDERS								
DYSPNEA	83 (27%)	55 (25%)	35 (24%)	173 (26%)	171 (29%)	108 (5%)	90 (28%)	369 (28%)
VASCULAR DISORDERS								
FLUSHING	79 (25%)	48 (22%)	40 (28%)	167 (25%)	87 (15%)	74 (17%)	54 (17%)	215 (16%)

Table 8: Summary of Hemodynamic Effects

Vital Sign Parameter[a]		Regadenoson n = 1337	Adenosine n = 678
Mean Change[b] in Heart Rate (bpm ± SD)		21 ± 11.9	15 ± 11.3
Mean Change[b] in Systolic Blood Pressure (mm Hg ± SD)		−3 ± 16.8	−7 ± 16.1
Mean Change[b] in Diastolic Blood Pressure (mm Hg ± SD)		−4 ± 9.0	−6 ± 9.6
Maximum Values			
Heart Rate	> 100 bpm	22.2%	13.0%
	> 120 bpm	2.8%	1.6%
Minimum Values			
Systolic BP	< 90 mm Hg	1.9%	2.8%
Diastolic BP	< 60 mm Hg	14.1%	17.6%
	< 50 mm Hg	2.4%	3.5%
Maximum Changes			
Heart Rate	Increase > 30 bpm	24.4%	11.8%
	Increase > 40 bpm	5.3%	2.9%
Systolic BP	Decrease > 15 mm Hg	39.1%	44.1%
	Decrease > 25 mm Hg	16.1%	18.0%
	Decrease > 35 mm Hg	6.9%	8.2%
Diastolic BP	Decrease > 15 mm Hg	19.3%	23.3%
	Decrease > 25 mm Hg	3.7%	5.3%

[a] Within 45 minutes after dosing

[b] Greatest change from baseline based on the mean value by time point.
Baseline values for the two treatment groups were similar, combined values as follows:
HR = 66 bpm
SBP = 137 mm Hg
DBP = 78 mm Hg

Table 9: Revised (Safety Update) Treatment Emergent ECG Changes

Abnormality	Regadenoson		Adenosine	
	At any time postdose	Within 16 minutes post dosing	At any time postdose	Within 16 minutes post dosing
Rhythm abnormality[a]	1.7%	0.8%	2.0%	1.9%
PACs	6.7%	4.9%	8.8%	6.1%
PVCs	14.0%	10.3%	12.2%	9.4%
1st degree AV block	2.8%	1.9%	7.0%	6.5%
2nd degree AV block	0.1%	0.1%	1.5%	1.5%
AV conduction abnormalities (other than AV block)	0.1%	0.1%	0	0
Ventricular conduction abnormalities	5.6%	3.8%	5.3%	3.2%
Ischemic ST segment changes	17.6%	16.5%	21.8%	21.4%
T wave abnormalities	38.0%	34.8%	37.3%	33.8%

[a] Includes atrial fibrillation/flutter, wandering atrial pacemaker, supraventricular arrhythmia, and ventricular arrhythmia

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Table 10: Treatment-Emergent ECG Abnormalities at Any Time Point Postdose and Within 16 Minutes Postdose, in the Original NDA and Safety Update (Gray boxes represent updated data)

Abnormality	Original NDA				Safety Update			
	Lexiscan		Adenosine		Lexiscan		Adenosine	
	At any time postdose	Within 16 minutes post dosing	At any time postdose	Within 16 minutes post dosing	At any time postdose	Within 16 minutes post dosing	At any time postdose	Within 16 minutes post dosing
Rhythm abnormality[1]	22/1266 (1.7%)	10/1250 (0.8%)	13/638 (2.0%)	12/632 (1.9%)	*26/1266 (2.1%)*	*13/1250 (1.0%)*	*14/638 (2.2%)*	12/632 (1.9%)
Ventricular arrhythmias	0/1266 (0%)	0/1250 (0%)	1/638 (0.2%)	1/632 (0.2%)	0/1266 (0%)	0/1250 0%)	1/638 (0.2%)	1/632 (0.2%)
PACs	85/1274 (6.7%)	62/1257 (4.9%)	57/645 (8.8%)	39/639 (6.1%)	*86/1274 (6.8%)*	62/1257 (4.9%)	57/645 (8.8%)	39/639 (6.1%)
PVCs	178/1274 (14.0%)	129/1257 (10.3%)	79/645 (12.2%)	60/639 (9.4%)	*179/1274 (14.1%)*	129/1257 (10.3%)	79/645 (12.2%)	60/639 (9.4%)
1st degree AV block	34/1209 (2.8%)	23/1193 (1.9%)	43/618 (7.0%)	40/612 (6.5%)	34/1209 (2.8%)	23/1193 (1.9%)	43/618 (7.0%)	40/612 (6.5%)
2nd degree AV block	1/1209 (0.1%)	1/1193 (0.1%)	9/618 (1.5%)	9/612 (1.5%)	1/1209 (0.1%)	1/1193 (0.1%)	9/618 (1.5%)	9/612 (1.5%)
AV conduction abnormalities (other than AV block)	1/1209 (0.1%)	1/1193 (0.1%)	0/618 (0%)	0/612 (0%)	1/1209 (0.1%)	1/1193 (0.1%)	0/618 (0%)	0/612 (0%)
Ventricular conduction abnormalities	64/1152 (5.6%)	42/1113 (3.8%)	31/581 (5.3%)	18/564 (3.2%)	64/1152 (5.6%)	42/1113 (3.8%)	31/581 (5.3%)	18/564 (3.2%)
Ischemic ST segment changes	223/1264 (17.6%)	206/1248 (16.5%)	139/638 (21.8%)	135/631 (21.4%)	223/1264 (17.6%)	206/1248 (16.5%)	139/638 (21.8%)	135/631 (21.4%)
T wave abnormalities	480/1264 (38.0%)	434/1248 (34.8%)	238/638 (37.3%)	213/613 (33.8%)	480/1264 (38.0%)	434/1248 (34.8%)	238/638 (37.3%)	213/631 (33.8%)

[1] Includes atrial fibrillation/flutter, wandering atrial pacemaker, supraventricular arrhythmia, and ventricular arrhythmia

12 APPENDIX II – ANALYSIS OF ADVERSE EVENTS BASED ON PATIENT WEIGHT

Figure 3: Histogram of Weights (Kg) for all patients in the Phase III Lexiscan studies.

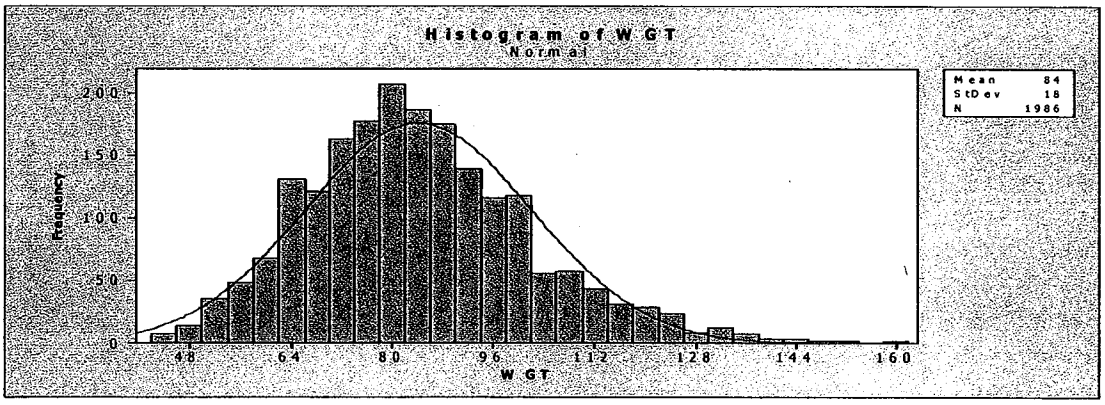

Figure 4: Histogram of Weights (Kg) for all male patients in the Phase III Lexiscan studies.

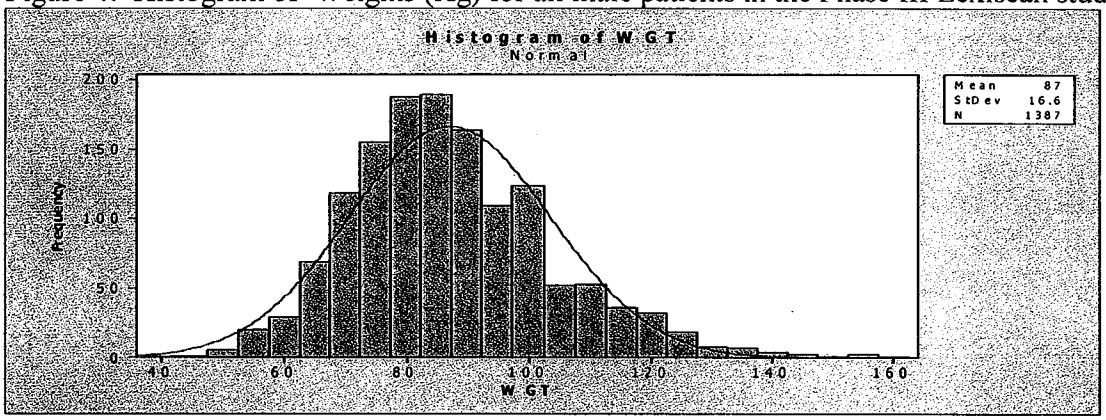

Figure 5: Histogram of Weights (Kg) for all female patients in the Phase III Lexiscan studies.

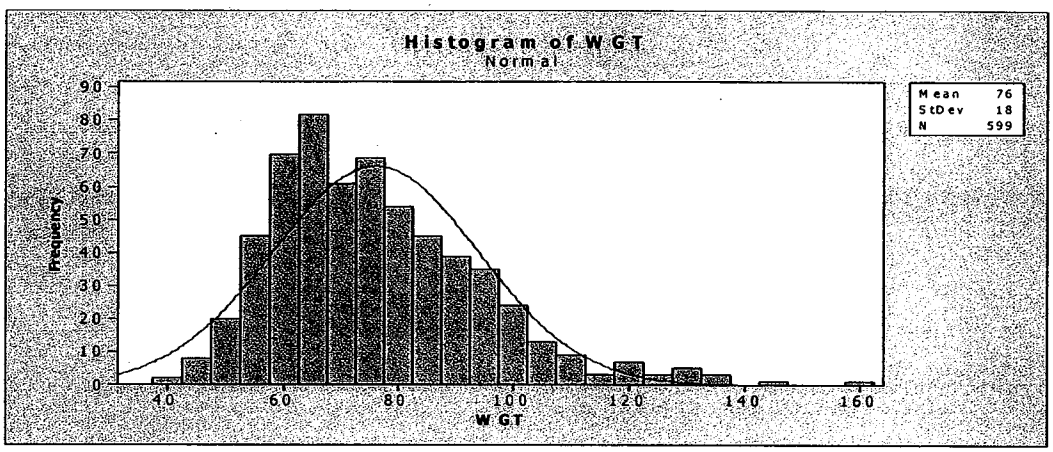

Table 11: AEs and Weight

System Organ Class Preferred Term	Adenosine Body weight < 60 kg (n=61; 16 male, 45 female)	Adenosine Body weight >= 60 kg (n=617; 451 male, 166 female)	Adenosine All (n=678)	Regadenoson Body weight < 60 kg (n=90; 24 male, 66 female)	Regadenoson Body weight >= 60 kg (n=1247; 917 male, 330 female)	Regadenoson All (n=1337)
CARDIAC DISORDERS						
ANGINA PECTORIS	7 (11%)	92 (15%)	99 (15%)	7 (8%)	123 (10%)	130 (10%)
GASTROINTESTINAL DISORDERS						
NAUSEA	7 (11%)	35 (6%)	42 (6%)	8 (9%)	78 (6%)	86 (6%)
ABDOMINAL DISCOMFORT	1 (2%)	13 (2%)	14 (2%)	9 (10%)	61 (5%)	70 (5%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS						
CHEST DISCOMFORT	6 (10%)	113 (18%)	119 (18%)	16 (18%)	152 (12%)	168 (13%)
CHEST PAIN	8 (13%)	61 (10%)	69 (10%)	12 (13%)	84 (7%)	96 (7%)
FEELING HOT	4 (7%)	50 (8%)	54 (8%)	7 (8%)	63 (5%)	70 (5%)
INVESTIGATIONS						
ELECTROCARDIOGRAM ST SEGMENT DEPRESSION	2 (3%)	43 (7%)	45 (7%)	3 (3%)	64 (5%)	67 (5%)
NERVOUS SYSTEM DISORDERS						
HEADACHE	12 (20%)	101 (16%)	113 (17%)	27 (30%)	315 (25%)	342 (26%)
DIZZINESS	0	46 (7%)	46 (7%)	7 (8%)	99 (8%)	106 (8%)
DYSGEUSIA	2 (3%)	43 (7%)	45 (7%)	6 (7%)	65 (5%)	71 (5%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS						
DYSPNOEA	13 (21%)	160 (26%)	173 (26%)	29 (32%)	340 (27%)	369 (28%)
VASCULAR DISORDERS						
FLUSHING	10 (16%)	157 (25%)	167 (25%)	10 (11%)	205 (16%)	215 (16%)

SOURCE: TAESUM_WEIGHT_FREQ (06JAN2007 12:37) ISS\Statistics\Set2\TABLE_GRAPH\TAESUM_WEIGHT_FREQ.RTF

Body Weight and Adverse Events (Patient groups <60 kg vs. ≥60 kg)

All patients (Lexiscan and adenosine) who were <60 kg tended to be older (mean 70 years old), were more likely to be female (74%), had a lower mean BMI (22.1 kg/m²), and had poorer renal function (53% had creatinine clearance <50 mL/min). A slightly smaller proportion of the patients <60 kg were Caucasian (66%) and slightly larger proportion were Asian (13%). Most of the patients (53%) weighing <60 kg were in the United States or Canada. In the relevant patient

population, Set 2, there were 90 Lexiscan patients (66 female and 24 males) with a body weight < 60 kg and 1,247 Lexiscan patients (330 females and 917 males) with a body weight ≥60 kg. The above graphs indicate there was a normal distribution of body weight, both for males and females.

AEs were compared by body weight base on the categories of <60 and ≥60 kg; similar percentages of patients weighing in these two weight categories in the Lexiscan group had AEs (83% for those < 60 kg vs. 79% for those ≥60 kg). The System Organ Class (SOC) of General Disorders and Administration Site Conditions had a higher percentage of patients who reported AEs in the <60 kg category (43% for those <60 kg vs. 27% for those ≥60 kg). This trend was similar in the preferred terms of chest discomfit and chest pain in this SOC for Lexiscan. A higher percentage of adenosine patients reported AEs in the General Disorders SOC than Lexiscan patients, but the reverse trend was observed with a higher percentage of the heavier adenosine patients reporting AEs (28% for those <60 kg vs. 38% for those ≥60 kg).

Changes in vital signs by body weight category were fairly similar for both weight categories within each psa treatment group. In the body weight category ≥60 kg, there was a slight trend towards a higher frequency of certain treatment-emergent ECK abnormalities:

- Rhythm abnormalities, PAC and PVCs occurred in 20.5% of patients in the body weight category of ≥60 kg compared to 14.9% of patients in the body weight category of <60 kg in Lexiscan patients.

In the body weight category <60 kg, another trend of treatment-emergent ECG abnormalities was noted:

- Ischemic ST segment changes occurred in 28.2% of patients compared to 16.9% in the body weigh category of ≥60 kg in Lexiscan patients.

The above summary indicates that minor associations exist between weight groups and certain minor AEs may exist. Dr Mucci, the statistical reviewer, has looked in detail at the important AEs of chest discomfort, angina and dyspnea (see table below). For these AEs no weight association exists.

Table 12: Combined Studies Principal Adverse Events by Weight

(I = Initial Scan ; F = Final (Randomized) Scan)

WGT Category (Kg's)	Arm	Agent	N	Angina	Chest Discomfort	Dyspnea
W < 60	A-A	I A	61	6 (10%)	6 (10%)	12 (20%)
		F A	61	7 (11%)	6 (10%)	13 (21%)
	A-R	I A	90	5 (6%)	18 (20%)	18 (20%)
		F R	90	7 (8%)	16 (18%)	29 (32%)
60≤ W < 80	A-A	I A	231	31 (13%)	41 (18%)	55 (24%)
		F A	231	31 (13%)	40 (17%)	53 (23%)
	A-R	I A	497	72 (14%)	74 (15%)	108 (22%)
		F R	497	55 (11%)	58 (12%)	121 (24%)
80≤ W < 100	A-A	I A	267	38 (14%)	38 (14%)	78 (29%)
		F A	267	43 (16%)	46 (17%)	73 (27%)
	A-R	I A	530	75 (14%)	81 (15%)	118 (22%)
		F R	530	48 (9%)	62 (12%)	143 (27%)
100≤ W < 120	A-A	I A	96	12 (13%)	14 (15%)	26 (27%)
		F A	96	15 (16%)	21 (22%)	24 (25%)
	A-R	I A	168	27 (16%)	36 (21%)	56 (33%)
		F R	168	20 (12%)	26 (15%)	59 (35%)
120≤ W	A-A	I A	23	2 (9%)	4 (17%)	10 (43%)
		F A	23	3 (13%)	6 (26%)	10 (43%)
	A-R	I A	52	4 (8%)	8 (15%)	22 (42%)
		F R	52	0 (0%)	6 (12%)	17 (33%)

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/s/

Ira Krefting
3/28/2008 10:25:28 AM
MEDICAL OFFICER

Libero Marzella
3/28/2008 05:00:23 PM
MEDICAL OFFICER