Appendix E – Review of Integrated Summary of Safety

The sponsor presented the safety data from the 8 phase 3 studies in 4 "pools."

Pool 1: placebo-controlled studies which used the 3 vardenafil doses (5, 10, and 20 mg) (studies 100249 and 10128)

Pool 2: placebo-controlled studies using both the 10 and 20 mg doses (studies 100249, 10128, 100250, and 100285)

Pool 3: placebo-controlled studies using vardenafil 5 mg, 10 mg, or 20 mg (studies 100249, 10128, 100250, 100285, and 10232)

Pool 4: all controlled and uncontrolled Phase 3 studies using vardenafil 5, 10, or 20 mg (studies 100249, 10128, 100250, 100312, 100285, 10232, 10125, and 10152)

The number of patients treated with placebo or vardenafil 5, 10, and 20 mg is shown in Table 1.

Table 1: Number of patients treated with placebo or vardenafil 5, 10, and 20 mg

Study	Placebo	Vard. 5mg	Vard. 10 mg	Vard. 20 mg
100249	182	193	199	188
10128	160	157	159	163
100250	143		36 (a)	30 (a)
100285	140		140	147
10232	168	170		
10125			513	509
10152				147
100312			167	161
Total	793	520	1214	1345

(a) These patients did not enter Study 100312 (extension of Study 100250)

Of the 3079 patients in the Phase 3 studies, 535 (17%) completed up to 12 weeks of exposure, 1087 (35%) completed between 12 and 24 weeks of exposure, and 1457 (47%) completed more than 24 weeks of exposure. The duration of exposure per dose in the Phase 3 studies pooled for safety (Pool 4) is shown in Table 2.

Table 2. Duration of exposure (Pool 4)

Study	>12 weeks to 24 weeks			>24 weeks to 48 weeks		
	5mg	10mg	20mg	5mg	10mg	20mg
100249	26	20	19	131	152	138
10128	119	128	120			
100250		14	13			
100312		66	67		85	85
100285		103	103			
10232	125					
10125		74	78		366	381
10152			12			119
Total	270	405	412	131	603	723

In Trials 100199 (Phase IIB trial), 100249, 10128, 100250, 100285, 10232, 10125, and 10152 combined, 667 patients received 5 mg, 1304 received 10 mg, and 1540 received 20 mg vardenafil. In the 4 primary efficacy studies and Trial 10232, 10125, and 10152, 520 patients received 5 mg, 1214 received 10 mg, and 1345 received 20 mg. With regard to the 20 mg dose, 995 patients received 20 mg for 6 months (Trials 10125, 10152, and 100249) and 392 patients received 20 mg for one year in Trial 10125).

Frequent adverse events:

Adverse events which were more common in patients on vardenafil than on placebo with an incidence of >2% on vardenafil are shown in Table 3.

Table 3. Incidence rates (%) of treatment-emergent adverse events reported by >2% of patients taking vardenafil, more frequent on vardenafil (Pool 3).

Adverse event	Placebo N=793	Vardenafil N=1812
Headache	5.5	15.6
Vasodilation	0.6	11.7
Rhinitis	3.8	10.3
Dyspepsia	0.8	3.9
Accidental injury	2.4	3.2
Sinusitis	0.8	3.1
Flu syndrome	2.3	2.7
Dizziness	0.9	2.4
Nausea	0.8	2.3
CK increased	1.1	2.0
Arthralgia	1.0	2.0

Reviewer's comment: Pool 3 includes Trial 10232. This Trial studied doses of placebo, 2.5 mg, and 5.0 mg vardenafil.

Within the vardenafil treatment subgroups by dose (Pool 2), the following adverse events were more common in the vardenafil 20 mg group than in the vardenafil 10 mg group: headache, vasodilation, rhinitis, dyspepsia, nausea, dizziness, and sinusitis. These adverse events rates are shown in Table 4.

Table 4. Incidence rates (%) by dose of treatment-emergent adverse events reported by >2% of patients taking vardenafil and more frequent on vardenafil than on placebo (Pool 2).

Adverse event	Placebo N=625	Vardenafil 10 mg N=650	Vardenafil 20 mg N=642
Headache	5.3	15.1	19.5
Vasodilation	0.6	12.5	14.2
Rhinitis	4.2	10.5	13.7
Dyspepsia	1.0	3.7	5.8
Sinusitis	0.8	2.6	4.4
Nausea	1.0	2.0	3.6
Dizziness	1.0	2.6	3.0

Reviewer's comments: Adverse events occurring in >2% of vardenafil patients were headache, vasodilation, rhinitis, dyspepsia, accidental injury, sinusitis, flu syndrome, dizziness, nausea, increase in CK, and arthralgia. These adverse events occurred more often on higher doses of vardenafil.

The incidence of drug-related adverse events (judged by the investigator as possibly or probably related to study drug) is shown in Table 5 (Pool 1).

Table 5. Incidence rates (%) by dose of drug-related treatment emergent adverse events reported by >2% of patients treated with vardenafil and more frequent on vardenafil than on placebo

Adverse event	Placebo N=342	Vard. 5mg N=350	Vard. 10 mg N=358	Vard. 20 mg N=351
Headache	2.0	8.0	11.7	17.4
Vasodilation	0.9	5.7	10.9	12.8
Rhinitis	0.9	1.1	6.7	7.7
Dyspepsia	0.3	2.0	2.8	6.0
Nausea	0.3	0.6	0.8	2.8
Dizziness	0.3	0.6	2.5	2.8

No case of accidental injury was reported as drug-related.

Effect of age on adverse events:

In the subgroup of patients >65 years of age, 173 patients received placebo and 405 patients received vardenafil in the placebo controlled studies. Overall, the incidence rates for adverse events in the >65 year old group were similar to those for the <65 year old group (56% versus 58%). The adverse events expected from this class of drugs (abnormal vision, back pain, dyspepsia, headache, rhinitis, and

sinusitis occurred less frequently in the > 65 year-old treatment group than in the <65 year-old treatment group. The incidence of vasodilation was similar in both age categories (12.35% in the >65 year old group and 11.51% in the <65-year-old group).

Reviewer's comment: These data indicate that older patients do not experience adverse events with higher frequency than younger patients.

Effect of race on adverse events:
The majority of patients in both the vardenafil and the placebo groups was Caucasian. Although the adverse event profile for vardenafil was consistent across subgroups by race, the number of patients within racial subgroups other than Caucasians was too small to detect any meaningful differences in the rates of adverse events across racial subgroups.

Effect of concomitant use of CYP 3A4 inhibitors:
In pool 3, only 7% of placebo patients and 6% of vardenafil patients used CYP 3A4 inhibitors. Although the numbers are low and no meaningful conclusions can be made, the incidence of adverse events was actually lower in the group who used CYP 3A4 inhibitors. Likewise, the use of CYP 3A4 substrate drugs did not increase the incidence rate of adverse events.

Reviewer's comment: Potent CYP3A4 inhibitors are likely to increase plasma levels of vardenafil substantially and dose adjustment should be recommended.

Effect of concomitant use of aspirin:
The incidence rates of bleeding were the same in patients taking aspirin and patients not taking aspirin (at aspirin doses 0 to 150 mg/day and >150 mg/day) in the placebo and vardenafil groups.

Common adverse events by treatment duration:
The greater rate of adverse events in the vardenafil group persisted for up to six months of treatment, but within this group the rate tended to decrease with time for all events except sinusitis. The onset of these adverse events was generally within the first 90 days of treatment.

Discontinuation rates (in relation to dose):

The discontinuation rates in relation to dose are shown in Table 6.

Table 6. Incidence rate by dose of treatment emergent adverse events leading to discontinuation of study medication (events with at least 2 cases in one treatment group) (Pool 1).

Adverse event	Placebo	Vard 5 mg N=350	Vard 10 mg N=358	Vard 20 mg N=351
Any event	7 (2%)	8 (2.3%)	9 (2.5%)	23 (6.6%)
Headache	0	3 (0.9%)	0	4 (1.1%)
Abdominal pain	0	0	1 (0.3%)	1 (0.3%)
Tachycardia	0	0	0	2 (0.6%)
Hypertension	0	1 (0.3%)	0	1 (0.3%)
Vasodilation	1 (0.3%	0	1 (0.3%)	1 (0.3%)
Abnormal LFT	1 (0.3%	0	3 (0.8%)	1 (0.3%)
Nausea	0	0	0	3 (0.9%)
Dizziness	0	1 (0.3%)	0	1 (0.3%)
Hypertonia	0	0	0	2 (0.6%)
Hypesthesia	0	0	2 (0.6%)	0
Rhinitis	0	0	1 (0.3%)	2 (0.6%)
Sweating	0	0	0	2 (0.6%)
Kidney stone	0	0	0	2 (0.6%)

Serious adverse events:

The incidence rates of serious adverse events are shown in Table 7 (Pool 1).

Table 7. Incidence rates by dose of serious treatment emergent adverse events (events with at least 2 cases in one treatment group) (Pool 1).

Adverse event	Placebo	Vard 5 mg N=350	Vard 10 mg N=358	Vard 20 mg N=351
Any event	18 (5.3%)	10 (2.9%)	11 (3.1%)	13 (3.7%)
Hernia	3 (0.9%)	0	1 (0.3%)	2 (0.6%)
Chest pain	2 (0.6%)	0	1 (0.3%)	0
Syncope	1 (0.3%)	1 (0.3%)	1 (0.3%)	0
Cholelithiasis	0	1 (0.3%)	1 (0.3%)	0
Diabetes	3 (0.9%)	0	0	1 (0.3%)
Hyperglycemia	0	1 (0.3%)	1 (0.3%)	0

The 2 cases of hyperglycemia occurred in patients with known diabetes.
One patient in the vardenafil 20 mg group experienced epistaxsis.

Deaths:

In the placebo-controlled studies, there was one death in the placebo group, one death in the 2.5 mg vardenafil group and one death in the sildenafil 50 mg group.

The patient in the 2.5 mg vardenafil group experienced a myocardial infarction 6 days after taking his last dose of study medication and 18 days after start of treatment. He died of multiple organ failure. The investigator did not consider the event related to study drug.

In uncontrolled studies and in ongoing studies, there were 3 additional deaths.

Patient 905-004 died suddenly one month after starting treatment in the extension study and 21 days after taking his last dose of vardenafil 10 mg. This 67-year-old man with a history of coronary artery disease and hypertension had EKG changes of inverted T waves and ST depression throughout the study. He failed to mention that he was taking nitroglycerin more frequently for chest pain. His last dose of study medication was 21 days before he died (confirmed by his wife). The investigator did not consider the death related to study drug.

Patient 38- 0590 committed suicide after learning that his wife was terminally ill with cancer.

Patient 035-40953 died of bronchogenic carcinoma prior to taking any study drug.

At the time of submission of the NDA, one additional patient in an ongoing study died. Patient 110-342 was a 69-year-old man who died in his sleep and was found unresponsive at home. An autopsy was performed and the cause of death determined to be cardiovascular disease secondary to diabetes and hypertension. The investigator deemed the cause of death unlikely related to study drug.

Hematological adverse events:

The incidence rates for treatment-emergent low hematologic laboratory values are shown in Table 8.

Table 8. Incidence rates (%) of low treatment emergent hematological laboratory values occurring in >2% of patients in a treatment group and more frequent in vardenafil than in placebo (Pool 3).

Laboratory value	Placebo N= 793	Vardenafil N=1812
Hematocrit	29/730 (4%)	69/1714 (4%)
Neutrophils – absolute count	12/581 (2.1%)	35/1560 (2.2%)

The incidence rates for potentially clinically significant low hemoglobin and hematocrit values were the same for the vardenafil and placebo groups. One case of thrombocytopenia was seen in the placebo group and one in the vardenafil group.

Chemistry parameters:

No substantial differences between groups were observed with respect to treatment-emergent high chemistry laboratory values. No chemistry finding had an incidence >2% higher in the vardenafil group than in the placebo group. Elevated CK, glucose, and LFT's occurred at rates >10%. The incidence rates of these values are shown in Table 9. (Pool 3).

Table 9. Incidence rates of elevated CK, glucose, AST, and ALT

	Placebo N=793	Vardenafil N=1812
CK	122/598 (20.4%)	313/1402 (22.3%)
Glucose	37/241 (15.4%)	80/487 (16.4%)
AST	57/698 (8.2%)	139/1630 (8.5%)
ALT	66/664 (9.9%)	159/1565 (10.2%)

The degree of elevation of CK, AST, and ALT in Pool 3 are shown in Table 10.

Table 10. Incidence rates of potentially clinically significant values of CK, AST, and ALT (Pool 3).

	Lab variable	Placebo	Vardenafil
CK	>3xULN	16/746 (2.1%)	50/1745 (2.9%)
	>5xULN	8/752 (1.1%)	18/1762 (1.0%)
	>10xULN	2/753 (0.3%)	5/1764 (0.3%)
AST	>3xULN	2/753 (0.3%)	4/1760 (0.2%)
	>5xULN	1/753 (0.1%)	3/1764 (0.2%)
	>10xULN	0/754	2/1765 (0.1%)
ALT	>3xULN	8/752 (1.1%)	4/1760 (0.2%)
	>5xULN	2/753 (0.3%)	2/1764 (0.1%)
	>10xULN	0/754	0/1765

In patients with elevated CK values, there was no direct correlation with clinical or EKG parameters. In no case of CK elevation greater than 3x ULN was the CK-MB fraction >2.5% of the total CK. Myalgia was reported in 12/1812 (0.7%) of the vardenafil patients compared with 2/993 (0.3%) of the placebo patients.
In Pool 3, 2 patients with clinically significant elevated CK values (one placebo and one 5 mg vardenafil) also had adverse events of myocardial ischemia. The vardenafil patient had ST-T changes suggestive of anterior ischemia on the Visit 5 EKG. Additionally, he had elevated CK values throughout the study and his concomitant medications included pravastatin. He saw his primary care physician who determined that the EKG findings and elevated CK values were "normal for this patient."

The serious adverse events related to abnormal CK or LFT values are shown in Table 11.

Table 11. Serious adverse events related to abnormal CK or LFT values (Pool 3).

	Placebo N=793	Vardenafil N=1812
LFT abnormal	0	2 (0.1%)
CK increased	0	1 (<0.1%)

The single serious adverse event related to an elevated CK (patient 040257) is discussed in Appendix N. This 49-year-old man had a CK level of 18690 U/L (normal 18-198 U/L). EKG showed no acute changes and there was no evidence of myoglobinuria. He had no chest pain. He did admit to acute muscle pain following an extensive workout in the gym 2 days prior to having his CK determined.

There were 2 patients with serious adverse events related to abnormal liver function tests. Both patients are discussed in Appendix N. One patient had an AST and ALT elevated at baseline and this reviewer believes that relationship to study drug is unlikely. The second (patient 004-0030) was a 62-year-old Asian man with history of hypertension, hypercholesterolemia, diabetes, hyperuricemia, hypokalemia, fluid retention, and "alcohol problems." Increased LFT's were diagnosed on Day 82 of the study on the basis of routine biochemistry tests. His ALT and AST had risen from 16 and 30 U/L at screening to 62 and 105 U/L on Day 82. He did not have any history of viral illness, cirrhosis, or other liver problems. The investigator considered that the increase in liver enzymes was likely related to the patient's alcohol consumption.

Reviewer's comment: Alcohol ingestion may have caused the elevated liver function tests, but relationship to study drug can not be entirely ruled out.

Cardiovascular safety:

Dizziness:

In Pool 3, dizziness was reported in 2.4% (43/1812) of vardenafil patients and 0.9% (7/793) of placebo patients. No patient in the vardenafil group versus one in the placebo group reported dizziness as a serious adverse event. The incidence of dizziness was higher in the vardenafil patients >65 years of age (3.2%) than in those <65 years (2.1%). The corresponding rates for the placebo patients were 0.6% and 1.0% for patients >65 and <65 years of age, respectively.

Syncope:

There were 4 cases of syncope reported in the placebo controlled studies (Pool 3). For the entire vardenafil pool (Pool 4) there were 6 cases of syncope in patients treated with vardenafil. Four of the 6 cases were reported as serious adverse events.

Patient 38-004 was an 80-year-old-man with a history of hypertension and hyperlipidemia who experienced a fainting episode on September 2, 2000. He was hospitalized for 48 hours for observation. He was taking blinded study drug (either

10 or 20 mg vardenafil) and concomitant medication was simvastatin. His last dose of study drug prior to the syncopal episode was on August 30, 2000. The investigator did not believe the event was related to study drug and he was continued in the study.

Patient 10125-111-142 was a 46-year-old Black male with a history of hypertension, osteoarthritis, myocardial infarction and a cardiac stent, paroxysmal atrial fibrillation, chronic sinusitis and fatigue who enrolled in the study in June, 2000. While at work on 9 Oct 2000, he experienced two episodes of pre-syncope with "precordial flutters" but no chest pain over approximately 10 minutes. The patient was hospitalized. ECGs were reportedly normal but troponin levels were elevated. His blood pressure was 101/60 mm Hg with a heart rate of 64 beats per minute. He had taken his last dose of blinded study drug (vardenafil 10 mg or 20 mg) on the day of the event. An acute coronary syndrome was suspected. Cardiac catherization revealed nonobstructive CAD with a hypertrophic, hyperdynamic left ventricle. A persantine-sestamibi study was reported as negative. The patient was discharged on antiplatelet and multiple antiischemic/antihypertensive medications. The event was considered not related to study drug. The patient continued the study, but eventually discontinued.

Reviewer's comment: The syncopal episode is temporally related to vardenafil ingestion and the relationship of drug to this event can not be excluded.

Patient 100249-027-008 was a 67-year-old Black male with a history of type 2 diabetes mellitus, hypertension, coronary artery disease with CABG, hypercholesterolemia, thrombocythemia and low white blood cell count who began taking vardenafil 10 mg in June, 2000. He experienced several syncopal episodes prior to hospitalization in Nov, 2000, and the last dose of study drug was taken 1 day prior to the episodes. During hospitalization he underwent cardiac catheterization and an elective PTCA was planned, however the patient did not follow through and he was discharged on digoxin (presumably for significant left ventricular dysfunction). His medical regimen also included lisinopril, metoprolol and furosemide which he was on prior to beginning study medication. He continued on study drug and completed the study in Jan 2001 but experienced mild episodes of syncope throughout the remainder of the study.

Reviewer's comment: The relationship of study drug to these events can not be excluded.

Patient 100249-044-057 was a 60-year-old man with a history of benign prostate hyperplasia, hypercholesterolemia, nephrolithiasis, lumbar compression fracture and myopia who took 5 doses of study drug (vardenafil 5 mg) between June 1, 2000, and June 7, 2000. He was hospitalized from 08 Jun 2000 to 10 Jun 2000 after an episode of syncope. He had taken a dose of study medication at 11:00 p.m. on June 7, 2000. On June 7 he also stopped taking terazosin and started finasteride. His blood pressure which had been normal during previous study

visits, was 92/50 mm Hg supine in the hospital on 10 June. His hemoglobin/hematocrit values (11.5/33.9) on June 8 were also lower than previous values (13-13.2/36-40). The syncopal event was considered as possibly related to study drug and the study drug was discontinued as of his last dose on June 7, 2000. At the termination visit on June 28, his BP, although normal (106/70), was still lower than previously and a 36 bpm increase in HR with no BP change was noted upon standing.

Reviewer's comment: The syncopal episode episode occurred within hours of the vardenafil dose. The fall in hematocrit is confounding.

Two cases of syncope were not reported as serious adverse events or adverse events leading to discontinuation.

Patient 10125-35-014 was a 77-year-old man with a history of hypertension, and hypercholesterolemia who was taking blinded study drug (vardenafil 10 mg or 20 mg) since 27 July 2000, with concomitant medications of cerivastatin 0.2 mg and enalapril 5 mg. On 11 Sep 2000 he had an episode of syncope late in the afternoon. He was referred to the emergency unit where a right bundle branch block (RBBB) was diagnosed. He was not hospitalized and the event was not considered study drug related. His last dose of study drug prior to the event was on 10 Sep 2000 at 21:00 hours. The patient continued in the study.

Patient 10128-032-040763 was a 57-year-old male with a history of type 2 diabetes mellitus, hypercholesterolemia, arthritis, and hypertension who was taking vardenafil 10 mg with concomitant medications of glimepiride 4 mg/day, hydrochlorothiazide 20 mg/day, rilmenidine phosphate 1 mg/day, metformin 850 mg/day, buflomedil hyrochloride 300 mg/day, insulin 22 U/day and 16 units/day and cerivastatin 0.3 mg/day. The patient fainted at Visit 2 while having a blood sample taken on June 29, 2000. This event was prior to the intake of any study medication. The patient completed the study.

An additional patient (10125-64-002) had a serious adverse event of a reported subarachnoid hemorrhage resulting from trauma during a syncopal event. This patient, who had a history of multiple sclerosis, was receiving 10 or 20 mg vardenafil and 3 days after his last dose, he experienced micturition syncope. The event was assessed as unlikely related to study drug and he continued in the study following hospital discharge.

Accidental injury:
Accidental injury was more frequent in the vardenafil treatment group (3.2%) than in the placebo group (2.4%) None of the accidental injuries was considered by the investigator to be drug related. Within the group of patients with accidental injuries, there was no dose effect, with 4.0%, 3.1%, and 3.1% of 5 mg, 10 mg, and 20 mg vardenafil patients, respectively, reporting accidental injuries compared with a rate of 2.6% in the placebo group. Accidental injury was reported as an adverse event for 5 vardenafil patients (0.3%) and for 3 placebo patients (0.4%). In

the vardenafil group, the percentage of accidental injuries in men <65 years of age was greater than in men >65 years of age (3.5% vs. 2.2%). Excluding "random encounters" (such as insect bites or stings), the rates of accidental injuries between the vardenafil and placebo groups was 2.8% and 2.3%. Sixty per-cent of accidental injuries occurred more than 72 hours after a dose of vardenafil.

Cerebrovascular accident:

Patients with a history of a cerebrovascular accident within the past 6 months were excluded from the vardenafil clinical trials. In the placebo-controlled studies, there was one CVA in the placebo group and none in the vardenafil group (Pool 3). In the entire vardenafil pool there were 3 cerebrovascular accidents reported.

Patient 10125-07-012 was a 63-year-old man with a history of hypertension who presented four days after his last dose of blinded study drug (vardenafil 10 or 20 mg) with right facial paralysis interfering with speech, and severe hypertension. He was hospitalized during which time his blood pressure normalized and the facial paralysis resolved. Study medication was resumed and the patient completed the trial. Relation to drug was deemed unlikely.

Patient 100312-28-040 was a 73-year-old man with a history of type 2 diabetes mellitus, hypertension, coronary artery disease and previous coronary artery bypass who was started on vardenafil 10 mg on 12 Oct 2000. On 26 Dec 2000, he developed weakness of the left upper extremity 2 days after his last dose of study medication (24 Dec 2000). He was hospitalized until 28 Dec 2000 during which time a CT scan showed evidence of previous left lacunar thalamic infarct but no new infarct. An ultrasound of the carotid showed bilateral plaque formation, without significant stenosis. The patient's symptoms resolved and the discharge diagnosis was transient ischemic attack. Although the relationship to drug was considered to be none, the study drug was discontinued permanently.

Patient 100312-28-014 was a 60-year-old Hispanic male with a history of type 2 diabetes mellitus and hypertension who developed symptoms of slurred speech, left hemiparesis, and headache while at work on 20 Nov 2000 and was hospitalized for two days. He had been taking vardenafil 10 mg since 01 Sep 2000 with his last dose being taken on the day before the event. Upon admission, he was in hypertensive crisis with a BP of 226/108 mmHg. During the study, the patient's blood pressures had been normal. A CT scan showed no evidence of intracerebral hemorrhage.The patient was discontinued from the study drug on 19 Nov 2000. Relationof the event to drug was considered as possible.

Reviewer's comment: Vardenafil ingestion occurred on the day prior to the event and relationship to drug is plausable.

Acute coronary insufficiency:

In the evaluation of acute coronary insufficiency, the sponsor considered serious adverse events and discontinuations due to adverse events relating to myocardial infarction and unstable angina. In the placebo controlled studies, myocardial infarction was reported in 1 patient treated with vardenafil and in 1 patient on placebo (Pool 3). Unstable angina was reported in 2 patients treated with vardenafil and in 1 placebo patient. In the entire vardenafil pool (Pool 4), there were 2 cases of myocardial infarction and 5 cases of unstable angina. The cases in patients taking vardenafil are summarized below.

Patient 100250-024-011 had a serious adverse event (SAE) of myocardial infarction. This 64 year old patient with a prior history of MI (PTCA x 3), diabetes, hypertension, hypercholesterolemia was hospitalized with atrial fibrillation and subsequently ruled-in for a non-Q-wave MI. His last dose of vardenafil 20 mg was 2 days before the event. The event was assessed as unlikely related to study drug and the patient completed the study.

Patient 100312-016-019 had an SAE of myocardial infarction and was discontinued from the study. This 62-year-old man with diabetes experienced an MI 13 days after his last dose of 20 mg vardenafil. The patient received a stent in his left anterior descending coronary artery. The event was assessed as unlikely related to study drug.

Patient 100250-017-009 had an SAE of coronary artery disorder and ST depression. This 64-year-old patient with diabetes and hypertension developed intermittent chest discomfort starting 2 days after taking his last dose of 10 mg vardenafil but continued taking drug. ECG several days later at the last scheduled visit revealed new ST depressions. The patient subsequently was diagnosed with CAD and underwent CABG. The event was assessed as possibly related to study drug.

Patient 100249-029-015 had an SAE of coronary occlusion. This 61-year-old patient with a history of valvular heart disease, cardiomegaly, and diabetes was admitted to the hospital with unstable angina 4 days after his last dose of 20 mg vardenafil. Significant CAD with LV dysfunction was found and the patient underwent CABG. The patient subsequently discontinued from the study. The event was assessed as unlikely related to study drug.

Patient 10125-39-010 had an SAE of unstable angina. This 55-year-old patient from Argentina with hypertension experienced unstable angina 5 days after taking his last dose of 10 or 20 mg vardenafil. The event was felt not to be drug related. The patient was discontinued from the study and there was no further follow up.

Patient 10125-120-008 had an SAE of coronary artery disorder. This 70 year-old patient with a history of CAD (PTCA 1986), recurrent atrial fibrillation, and smoking underwent coronary angiography 4 days after his

last dose of 10 or 20 mg vardenafil and was found to have significant CAD. He received medical treatment with long-acting nitrates and no further vardenafil. About 1 week later he was admitted to the hospital with chest pain and underwent CABG. The event was assessed as not drug related.

Patient 10125-105-362 had an SAE of cardiovascular surgery and was discontinued from the study. This 61-year-old patient with a history of hypertension developed shortness of breath and chest tightness with elevated cardiac enzymes 3 weeks after his last dose of vardenafil 10 or 20 mg. He subsequently underwent CABG and his postoperative course was complicated by pulmonary embolus and thrombophlebitis. No events were felt to be drug related.

In addition to these patients, there were several cases that were suspicious for acute coronary ischemia during the treatment period. Two cases (one vardenafil – Patient 10128-004-040084 and one placebo – Patient 10232-001-0004) occurred in the placebo-controlled trials. Patient 10128-004-040084, who received vardenafil 10 mg was reported to have an SAE of chest pain and treated with nitrates. A cardiac workup was pending. In Pool 4 the case of Patient 10125-111-142 is suspicious for an acute coronary syndrome. This patient was previously discussed above in the section on syncope.

In addition to those cases reported as serious adverse events and discontinuations, there were several cases of myocardial infarction that resulted in deaths. Patient 100312-905-004 died suddenly 21 days after his last dose of 10 mg vardenafil from a presumed myocardial infarction. Patient 10232-013-0004 on vardenafil 2.5 mg died from multiple medical complications after suffering a myocardial infarction 6 days after his last dose of study medication. Patient 10128-001-040348 on sildenafil 50 mg died from a myocardial infarction shortly after sexual intercourse. In on-going study 10125, Patient 10125-110-342 on vardenafil 10 or 20 mg died in his sleep from a presumed cardiac cause.

IND Safety reports submitted during the review process included the following case:

Patient 10566/38019 (from ongoing investigation of efficacy and safety of vardenafil 20 mg in comparison to sildenafil 100 mg in patients with diabetes, hypertension, or hyperlipidemia). This 62-year-old man had a history of diabetes, coronary artery disease, hypertension, and hypercholesterolemia. He had undergone a coronary angioplasty in 1993 and angioplasty with stent in 1996. Concomitant medications were atenolol, amlodipine/benazepril, Pravachol, and previously taken Viagra (discontinued on January 26, 2001). On March 16, 2002, approximately one hour after the first dose of study drug (vardenafil 20 mg), he experienced severe chest pain. His symptom of chest pain began approximately 20 minutes after intercourse. He was admitted to the hospital, diagnosed with myocardial infarction, and underwent triple coronary artery bypass. After initially

arriving at the hospital, he had experienced ventricular fibrillation and was defibrillated into sinus rhythm. According to the patient, he had taken one dose of study drug, however, 15 doses were returned instead of 19. The sponsor made attempts to contact the patient to verify drug accountability, but the patient "did not have time to talk."

Cardiovascular safety (electrocardiography):
Preclinical electrophysiology: In vitro testing using a whole cell patch clamp model showed that vardenafil (as well as sildenafil) has the potential to affect the outward repolarization current via HERG blockade. The IC_{50} of vardenafil was 30 uM and the IC_{50} of sildenafil was 47 uM. In terms of the threshold concentration for HERG blockade, the value for vardenafil was 3 uM. The IC_{50} and threshold concentrations represent values approximately 15000 and 1500 fold, respectively, above the maximum concentration of vardenafil following a 20 mg dose based on free plasma concentration.

Clinical QT analysis: In 8 single-dose and 2 multiple-dose clinical pharmacology studies, EKG's were evaluated for QT changes. Doses of vardenafil from 5 to 80 mg were studied. EKG's in these studies were machine read. The interpretation of the QT interval data is complicated by the fact that vardenafil increases heart rate. The EKG's in these studies were subsequently manually read and the data included in Appendix 18.1 of the ISS. The QT data and particularly the QT data in the key studies 10010 and 10011 are separately reviewed in Appendix M.

Visual safety:
Clinical pharmacology study 10197 focused on determining the effects of vardenafil on vision. Study 10197 was a Phase 1 double-blind, cross-over study in 24 healthy male volunteers. These volunteers were tested before and after a single dose of 40 mg vardenafil to assess the drug's effect on the following parameters: refraction, fundoscopy, visual acuity, intraocular pressure, slit-lamp, Humphrey 30-2 visual field tesst, Amsler grid test, Farnsworth-Munsell 100 Hue test, and electroretinography (ERG). The sponsor believes that the most pronounced differences between active and placebo groups occurred in the Farnswoth-Munsell 100 test were observed for total error score at 1 and 6 hours after drug administration. The findings did not correlate with vardenafil plasma levels. The sponsor believes that the data indicate a mild and transient impairment of color discrimination in the blue/green and purple ranges on vardenafil.ERG measurements showed reductions of the cone driven b-wave amplitude with recovery after 24 hours. Across all placebo controlled trials of 5, 10, and 20 mg vardenafil (Pool 1), chromatopsia was reported in 1 patient. This patient had transient blue visual disturbance. The treatment-emergent adverse events related to the eye or vision that occurred in Phase 3 placebo-controlled trials (Pool 3) are shown in Table 12.

Table 12. Treatment-emergent adverse events related to the eye or vision (Pool 3)

Visual event	Placebo N=793	Vardenafil N=1812
Conjunctivitis	2 (0.3%)	16 (0.9%)
Abnormal vision	2 (0.3%)	11 (0.6%)
Amblyopia	1 (0.1)	7 (0.4%)
Photophobia	0	7 (0.4%)
Eye hemorrhage	0	5 (0.3%)
Lacrimation disorder	0	5 (0.3%)
Cataract	0	4 (0.2%)
Eye pain	0	3 (0.2%)
Dry eyes	0	2 (0.1%)
Glaucoma	0	2 (0.1%)
Chromatopsia	0	1 (<1%)
Corneal lesion	0	1 (<0.1%)
Eye disorder	0	1 (<0.1%)
Mydriasis	0	1 (<0.1%)
Refraction disorder	0	1 (<0.1%)
Retinal disorder	0	1 (<0.1%)
Retinal hemorrhage	0	1 (<0.1%)
Blindness	1 (0.1%)	0
Vitreous disorder	1 (0.1%)	0

Six patients (0.2%) of the 3079 patients exposed to vardenafil discontinued due to a visual related adverse event. The only serious adverse event was 1 case of glaucoma.

Reviewer's comment: An ophthalmology consultation concerning the possible eye effects of vardenafil was obtained. The ophthalmologic consultant concluded that: "From an ophthalmologic perspective, there is no objection to the approval of this NDA provided that the labeling is consistent with other phosphodiesterase inhibitors. It is recommended that repeated dose studies evaluating the effect of vardenafil on retinal function be conducted and submitted for review."

Priapism:

There were no reports of priapism occurring in vardenafil patients in any study of vardenafil 5, 10, or 20 mg. Two cases were reported as priapism in the clinical pharmacology studies in patients taking 40 mg vardenafil. The 2 events were described as intermittent full erection and painful erection.

Appendix F – Clinical Trial 10125 (A randomized, double-blind, multicenter, fixed-dose, parallel group twelve month study to investigate the safety and tolerability of the phosphodiesterase type 5 inhibitor BAY 38-9456 in the treatment of patients with erectile dysfunction) (Trial began April 6, 2000 and ended August 27, 2001)

F.1 Objective: The objective of this study was to assess the safety, tolerability, and efficacy (descriptive comparison only) of two doses of the phosphodiesterase type 5 inhibitor vardenafil in men with erectile dysfunction for up to 12 months.

F.2 Design and conduct summary: This was a multicenter, randomized, double-blind, fixed-dose, 2-arm, parallel comparison of 10 mg and 20 mg vardenafil in men with ED. (In order to maintain blinding, patients also received placebo of the corresponding other vardenafil dose.) The overall design consisted of a 4-week baseline (no treatment) period, a 52-week double-blind treatment period, and a follow-up period of 7 days to collect data concerning serious adverse events.

One thousand twenty patients were enrolled at 72 sites in Argentina, Australia, Brazil, Canada, Chile, Germany, Israel, Mexico, South Africa, Spain, and the United States. Patients were seen at screening, randomization, and at months 1, 2, 3, 6, 9, and 12. The primary goal of the study was to compare the safety and tolerability of two doses of vardenafil. The patient was instructed to take study medication about 1 hour prior to intended sexual intercourse. Safety and tolerability were assessed on grounds of laboratory evaluation (hematology, chemistry, and urinalysis), physical examination, eye examinations (North American patients only), blood pressure, heart rate, adverse events, and ECG's. No formal statistical tests were performed for safety variables. Secondary endpoints included efficacy as measured by the EF domain score of the IIEF and SEP questions concerning the ability to penetrate and maintain an erection. In the applicable US sites, at the eye examination preceding Visit 8, patients were instructed to receive one dose of study medication approximately one hour before the visual acuity and the Farnsworth-Munsell 100 examination.

F.3 Study population: The study population was men older than 18 years with a history of erectile dysfunction for >6 months. Baseline characteristics of the study population are shown in Table 1.

Table 1. Baseline characteristics of the study population.

	Vardenafil 10 mg N=514	Vardenafil 20 mg N=506
Age (years) (mean)	56.3	55.5
Race		
Caucasian	444 (86%)	454 (90%)
Black	35 (7%)	23 (5%)
Asian	5 (<1%)	3 (<1%)
American Indian	1 (<1%)	2 (<1%)
Hispanic	5 (<1%)	5 (<1%)
East Indian	1 (<1%)	0
Mestizo	23 (4%)	19 (4%)
Hypertension	167 (32%)	160 (32%)
Diabetes	97 (19%)	99 (20%)
Myocardial infarction	16 (3%)	12 (2%)
Coronary bypass surgery	12 (2%)	15 (3%)
EF Domain of IIEF (mean)	13.1	13.1

Approximately 60% of patients had previously taken sildenafil.

F.4 Inclusion and exclusion criteria: Inclusion criteria included: 1) men with ED for more than 6 months 2) age 18 years or greater 3) patient must make at least 4 attempts at sexual intercourse during the unmedicated baseline period, and at least 50% of attempts during this period must be unsuccessful (at least one of the questions relating to penetration and maintenance must be answered no). Exclusion criteria included: 1) presence of penile anatomical abnormality 2) erectile dysfunction after spinal cord injury 3) history of radical prostatectomy that is not documented to be bilaterally nerve sparing and that is not associated with residual pudendal nerve function 4) retinitis pigmentosa 5) history of positive test for hepatitis B or C 6) symptomatic chronic heart disease (New York Heart Association Class II or greater) (deleted by amendment 2) 7) unstable angina pectoris 8) history of myocardial infarction, stroke, ECG evidence of ischemia (except stable angina) or life-threatening arrhythmia within the prior 6 months 8) Added by amendment 7 – In centers in Israel only, patients with coronary heart disease will not be excluded. In case of newly diagnosed angina or heart disease occurring during the study, the patient will be excluded from continuing the study and referred to a cardiologist 9) uncontrolled atrial tachyarrhythmia at screening 10) severe chronic liver disease or AST or ALT >3 times ULN 11) Clinically significant chronic hematologic disease or bleeding disorder 12) history of significant peptic ulcer within one year of visit 1 13) resting hypotension (a resting systolic blood pressure of <90 mmHg) or hypertension (a resting systolic blood pressure of >170 mmHg or a resting diatolic blood pressure of >110 mmHg) 14) symptomatic postural hypotension within 6 months prior to Visit 1 15) uncontrolled diabetes mellitus (hemoglobin

A_{1c} > 12%) 16) inadequately treated hyperthyroidism or hypothyroidism 17) history of cancer within the past 5 years (other than basal or squamous skin cancer) 18) patients were excluded if they were taking any of the following: nitrates or nitric oxide donors, trazodone (amendment 2 allowed erythromycin and rifampin), anticoagulants with the exception of anti-platelet drugs, androgens or antiandrogens (amendment 2 allowed ketoconazole), Viagra within 7 days of Visit 1, protease inhibitors, ketoconazole, itraconazole, ritonavir, or indinavir (20 mg treatment only) (amendment 9) 19) serum testosterone level below lower limit of normal according to involved laboratory 20) serum creatinine >2.5 mg/dL 21) history of severe migraine headaches occurring once monthly or more frequently within the past 6 months 21) history of unresponsiveness to sildenafil or significant side effects leading to discontinuation of sildenafil (amendment 1).

F.5 Primary and secondary endpoints: The primary endpoints (objectives) were safety and tolerability. The following safety assessments were performed during the trial: 1) hematology, chemistry, and urinalysis at Months –1, 0 1, 3, 6, 9, and 12 2) physical examination at screening and Months 3 and 12 3) supine and standing blood pressure and pulse at all visits 4) data regarding AE's at all visits 5) 12 lead EKG at screening and at Months 3, 6, and 12 6) eye examinations (USA and Canada only) at randomization and Months 3 and 12. One dose of study medication was used for the eye examination dosing test and was to be taken 1 hour before testing. The assessment of efficacy was a secondary endpoint (objective) of the study.

F.6 Withdrawals, compliance, and protocol violations:

Out of 1367 patient screened, 1020 patients were randomized. Of these 1020 patients, 514 were randomized to the vardenafil 10 mg group and 506 to the vardenafil 20 mg group. A total of 755 patients (74%) completed the study: 363 (71%) in the vardenafil 10 mg group and 392 (77%) in the vardenafil 20 mg group. In the vardenafil 10 mg group, 26 (5%) withdrew because of an adverse event and in the vardenafil 20 mg group, 34 (7%) withdrew because of an adverse event. Three patients were excluded from all analyses because they had received treatment with both the 10 and 20 mg doses. One of these patients experienced a serious adverse event (he underwent vasectomy).

F.7 Efficacy analysis:

The IIEF erectile function domain score and SEP items #2 and 3 (insertion and maintenance questions) were the criteria of primary interest. "Although statistical analysis was performed, the "p-values are to be interpreted as descriptive parameters. No statistical conclusions about efficacy were to be drawn from the results." Efficacy data are shown in Table 2.

Table 2. Efficacy data

	Vardenafil 10 mg N=500	Vardenafil 20 mg N=502
EF domain of IIEF		
Baseline	13.0	13.2
Week 52 (LOCF)	22.6	23.9
Change from baseline	9.6	10.7
Penetration possible (%)		
Baseline	45.1	42.3
Week 52 (LOCF)	84.5	87.5
Change from baseline	39.4	45.3

Although only descriptive statistics were performed for the efficacy analysis, the effect of vardenafil appears to be maintained at 52 weeks.

F.8 Safety analysis:

All randomized patients who had taken at least one dose of study medication were included in the safety analysis. For all safety analyses, descriptive statistics were performed; no formal statistical testing of safety data was performed.

F.8.1 Extent of exposure:

The extent of exposure by treatment duration is shown in Table 3.

Table 3. Treatment duration (safety population)

Duration (days)	Vardenafil 10 mg N=514	Vardenafil 20 mg N=506
Mean	278	293
Median	343	346
<7	16 (3%)	13 (3%)
7-30	23 (4%)	22 (4%)
30-60	24 (5%)	16 (3%)
60-90	26 (5%)	16 (3%)
90-180	37 (7%)	28 (6%)
180-270	20 (4%)	21 (4%)
270-360	245 (48%)	266 (53%)
>360	121 (24%)	124 (25%)

The mean number of doses per week was 2.3 and 2.4 in the 10 and 20 mg vardenafil groups, respectively. Overall doses (mean) in the 10 and 20 mg vardenafil groups was 95.4 and 102.6, respectively.

F.8.2 Serious adverse events:

Deaths: There were 2 deaths during the study.

One death occurred during screening (patient 39-1020). The other patient (# 110-342) died of cardiovascular disease after 8 months of treatment. The relationship to study drug was assessed as "unlikely."

Patient 110-342 was a 69-year-old man with a history of hypertenion, diabetes, peripheral neuropathy, urinary incontinence, benign prostatic hyperplasia, and hyperlipidemia. Concomitant medications were indapamide, gabapentin, glipizide, potassium, nifedipine, and oxybutynin. Before his seventh visit (Day 253), the study co-ordinator was notified that he had died. He died in his sleep and was found unresponsive at home. An autopsy was performed, and the death was "probably caused by complications of cardiovascular disease secondary to diabetes and hypertension. "No other information is available." The autopsy report is "not yet available." No information concerning temporal relationship of drug intake and death is provided.

Serious adverse events:

The number of serious adverse events in the 2 treatment groups is shown in Table 4.

Table 4. Serious adverse events (n (%))

	Vardenafil 10 mg	Vardenafil 20 mg
Serious adverse events	35 (7%)	42 (8%)

Serious adverse events by treatment group are shown in Table 5.

Vardenafil 10 mg	Vardenafil 20 mg
Renal stone	Seizures
Lumbar disc	Syncope (# 38-004)
Angina (# 38-015)	Prostate cancer
Unstable angina (#39-010)	Vasectomy
Angina (#40-006)	Hip surgery
Knee operation	Cholelithiasis
Shoulder surgery	Elevated SGOT (# 47-003)
Angina pectoris (#29-003)	Varicose vein surgery
Nasal sinus surgery	Arrythmia during nasal surgery (# 903-098)
Ureteral stone	Shoulder surgery
Anemia and thrombocytopenia (#13-016)	Spine surgery
Stroke (#14-005)	Knee surgery
Leg thrombosis	Knee surgery
Ureteral stone	Colon cancer

Cataract surgery	Chronic back pain
Knee operation	Hypertension
Knee pain	Knee operation
Ankle fracture and atrial fibrillation	Tonsillectomy
Appendicitis	Cholecystitis
Cataract surgery	Nasal surgery
Cholecystitis	High GGT/low platelets (# 18-015)
Foot fracture	Colon polyps
Stroke (# 07-012)	Cholecystectomy
Stroke and syncope (# 64-002)	Rehabilitation for ?
Degenerative arthritis	Chest pain (# 59-001)
Elevated LFT's and angina (# 105-258)	Vasectomy
Shortness of breath and bypass surgery	Bladder tumor
Ptosis right eye	Renal colic
Cholelithiasis	Increased CK and CK-MB (# 06-005)
Syncope (# 111-142)	Psychotic syndrome
Inguinal hernia	Chronic back pain
Coronary artery disease (# 120-008)	Facial trauma
Glioblastoma	Melanoma
	Foot trauma
	Bladder cancer
	Neuralgia
	Renal stones
	Hip surgery
	Coronary artery bypass graft
	Cataract
	Arthritis
	Malignant pleural effusion
	Ankle surgery
	Inguinal hernia

Narratives for patients # 39-010, 38-004, 07-012, 64-002, 111-142, and 120-008 are provided in Appendix E (integrated summary of safety). Narratives for patients # 47-003, 105-258, and 06-005 are provided in Appendix N.

Patient 13-016 had thrombocytopenia at screening.

Patient 14-005 (64-year-old) (10 mg vardenafil) was hospitalized for a stroke which occurred on October 30, 2000. Last study medication was on October 26, 2000.

Patient 18-005 had abnormal GTT and low platelet count at screening.

Patient 38-015 was hospitalized for angina on April 3, 2001. His last dose of study medication (10 mg vardenafil) was on March 21, 2001.

Patient 29-003 was hospitalized for angina in June, 2001, after having undergone an angioplasty on June 19, 2001. The date of last study medication intake is not recorded.

F.8.3 Discontinuations secondary to adverse events:

Adverse events led to study discontinuation in 55 patients (5%): 26 (5%) in the 10 mg group and 29 (6%) in the 20 mg group. Patients >65 years of age showed a higher drop-out rate on vardenafil 20 mg than with 10 mg (9 (10%) versus 3 (3%)). Headache was the reason for 7 patients to discontinue the study prematurely.

F.8.4 Frequent adverse events:

The incidence rates of treatment-emergent adverse events are shown in Table 6.

Table 6. Incidence rates of treatment emergent adverse events (frequency >2% or related to vision disorders)

	Vardenafil 10 mg N=514	Vardenafil 20 mg N=506
Headache	79 (15%)	112 (22%)
Vasodilation	62 (12%)	87 (17%)
Rhinitis	61 (12%)	70 (14%)
Accidental injury	17 (3%)	26 (5%)
Flu syndrome	18 (4%)	25 (5%)
Dyspepsia	27 (5%)	36 (7%)
Pharyngitis	21 (4%)	17 (3%)
Bronchitis	9 (2%)	14 (3%)
Dizziness	17 (3%)	13 (3%)
Hypertension	22 (4%)	21 (4%)
Nausea	15 (3%)	11 (2%)
Diarrhea	12 (2%)	11 (2%)
Creatine phosphokinase increased	17 (3%)	19 (4%)
Arthralgia	11 (2%)	12 (2%)
Abnormal vision	8 (2%)	13 (3%)
Amblyopia	5 (1%)	6 (1%)
Chromatopsia	1 (<1%)	4 (1%)

Reviewer's comment: The rates for headache and vasodilation were greater in the 20 mg vardenafil group than in the 10 mg vardenafil group.

The incidence of drug-related treatment emergent adverse events with a frequency of >2% is shown in Table 7.

Table 7. Incidence of drug-related treatment emergent adverse events with a frequency of >2%.

	Vardenafil 10 mg N=514	Vardenafil 20 mg N=506
Headache	79 (14%)	101 (20%)
Vasodilation	59 (11%)	86 (17%)
Rhinitis	38 (7%)	55 (11%)
Nausea	12 (2%)	9 (2%)
Dyspepsia	22 (4%)	31 (6%)
Gastritis	5 (1%)	8 (2%)
CK increased	7 (1%)	10 (2%)
Sinusitis	3 (1%)	8 (2%)
Conjunctivitis	10 (2%)	4 (1%)
Abnormal vision	6 (1%)	11 (2%)
Dizziness	16 (3%)	10 (2%)

F.8.5 Clinically significant events:

Stroke was reported as a serious adverse event in 2 patients (#'s 14-005 and 07-012). Both patients had received 10 mg vardenafil. The relationship to study drug was assessed by the investigator as "unlikely" for patient 07-012 and as "none" for patient 14-005. An additional patient experienced a subarachnoid hemorrhage. He had been on the 10 mg dose and relationship to study drug was rated by the investigator as "unlikely." Another patient (#10-633) experienced a transient ischemic attack during run-in and was not randomized.

F.8.6 Changes in laboratory values:

The incidence rates of selected treatment-emergent laboratory abnormalities with values above the upper limit of normal which occurred in >5% of patients in either of the two treatment groups are shown in Table 8.

Table 8. Number (%) of patients with high treatment-emergent laboratory abnormalities observed in >5% of patients.

	Vardenafil 10 mg	Vardenafil 20 mg
Calcium	29/496 (6%)	23/489 (5%)
Creatinine	30/473 (6%)	22/458 (5%)
AST	40/467 (9%)	55/457 (12%)
ALT	51/443 (12%)	57/430 (13%)
GGT	38/436 (9%)	30/423 (7%)
Creatine kinase	76/377 (20%)	63/367 (17%)

There were 31 patients with creatine kinase levels >3X ULN in the vardenafil 10 mg group and 28 patients with creatine kinase levels > 3X ULN in the vardenafil 20 mg group. The highest CK increase was 4030 U/L in a patient receiving vardenafil 20 mg (patient #112-341). This patient had practiced weight lifting prior to blood collection. The second highest CK increase was 2884 U/L in a

patient receiving 10 mg vardenafil. This patient underwent intense physical exercise prior to blood collection. In another patient (# 18-004) CK elevations were associated with repeat intramuscular injections.

Reviewer's comment: No cases of rhabdomyolysis or myopathy were reported as adverse events in these patients. Acute myocardial infarction was excluded as the cause of the elevated CK's. One patient was withdrawn from the study because of an increase in CK (patient # 45-014).

The number (%) of patients with selected low treatment-emergent laboratory abnormalities observed in >3% of patients is shown in Table 9.

Table 9. Number of patients (%) with selected low treatment-emergent laboratory abnormalities observed in >3% of patients.

	Vardenafil 10 mg	Vardenafil 20 mg
Hematocrit	14/500 (3%)	14/495 (2%)
Platelets	15/495 (3%)	10/491 (2%)

Study drug was discontinued in 3 patients because of laboratory abnormalities. Patient #45-014 had a 1X increase in CK assessed by the investigator as not drug related. Patient # 33-017 had a 2X increase in liver function tests (10 mg vardenafil) judged as "possible" relationship to study drug and patient # 13-026 with a 2X elevation in liver function tests judged as "no relationship" to study drug.

F.9 Reviewer's assessment of efficacy and safety: In this one year study, 363 patients on vardenafil 10 mg completed the study and 392 patients on 20 mg vardenafil completed the study. Although cardiovascular adverse events did occur, all but a few cases did not temporally occur with vardenafil intake. This reviewer believes that the results of this trial support the efficacy and safety of vardenafil for the treatment of erectile dysfunction.

Appendix G: Trial 10152 ("An open, single-group, multicenter, fixed dose, six month study to investigate the safety and tolerability of the phosphodiesterase type V inhibitor BAY-38-9456 in the treatment of patients with erectile dysfunction") (Start date – 6/14/2000; ending date – 5/9/2001).

G.1 Objective: To assess the safety and tolerability of one dose of vardenafil (20 mg) for 6 months in men with erectile dysfunction.

G.2 Design and conduct: This was an open label, single-dose (20 mg vardenafil), multicenter, study (some of the patients were continued from Phase 2b study 100199 and some were "de novo" patients). Fifty-seven centers enrolled patients (19 in Germany, 3 in Belgium, 10 in France, 2 in the Netherlands, 2 in Poland, 4 in South Africa, 3 in Portugal, 1 in Hungary, and 13 in the United States. 640 patients entered the baseline period, 574 patients entered the 20 mg vardenafil treatment phase, and 494 completed the entire 6-month study. Patients were seen at Months –1, randomization (M0), and months 1, 2, 3, and 6. The primary objective (endpoint) was the evaluation of safety. Safety was evaluated in the following treatment groups: 1) patients who completed Phase 2b study 100199 and had been assigned to placebo 2) patients who completed the phase 2b study and were assigned to vardenafil and 3) "de novo" patients. The sponsor intentially tried to redruit 50% diabetics in the "de novo" group.

G.3 Study population: The study population included men over the age of 18 years with erectile dysfunction for 6 months. Approximately 90% of the patients were Caucasian, 3% Black, 3% Asian, and 2% Hispanic.

G.4 Exclusion criteria: Exclusion criteria included: 1) erectile dysfunction after spinal cord injury 2) radical prostatectomy 3) unstable angina pectoris 4) history of myocardial infarction or stroke within prior 6 months 5) resting hypotension (systolic blood pressure of < 90 mmHg) or hypertension (resting systolic blood pressure of >170 mmHg or a resting diastolic blood pressure of > 110 mmHg) 6) symptomatic postural hypotension within 6 months of Visit 1 7) uncontrolled diabetes (hemoglobin A1c > 12%) 8) concomitant nitrates or nitric oxide donors 9) serum creatinine > 2.5 mg/dL and 10) AST or ALT > 3X ULN.

G.5 Efficacy: This was an open-label, single dose trial and efficacy measurements were secondary endpoints. Although no formal analysis was performed and there is no control group, the efficacy measured by ED domain of the IIEF and penetration and maintenance questions appears to be maintained throughout the entire 6 month study period.

G.6 Safety:

G.6.1 Extent of exposure: The mean treatment duration in days was 164 and the mean total number of doses taken during the study was 68.

G.6.2 Serious adverse events:

Deaths: One death (patient # 38-0590) occurred during the study. The death was from suicide and the investigator believed that it was not due to study medication.

Serious adverse events: Twenty-two patients experienced serious adverse events (overall incidence of 4%): abdominal pain (1), accidental injury (2), asthenia (1), surgery (1), chest pain (2), malaise (1), suicide attempt (1), arrhythmia (1), atrial fibrillation (2), carotid occlusion (1), myocardial ischemia (1), syncope (1), vascular anomaly (1), digestive surgery (1), ileus (1), pancreatitis (1), hyperglycemia (1), arthralgia (1), arthritis (1), musculoskeletal surgery (1), myalgia (1), dizziness (1), dyspnea (1), interstitial pneumonia (1), melanoma (1), glaucoma (1), prostate cancer (1), unintended pregnancy (1), and urinary incontinence (1).

Patient # 013-84 experienced syncope. The investigator rated this event as not being related to study drug. The event occurred on December 21, 2001, and the last dose of study drug was taken on December 20, 2001. The patient regained consciousness quickly and suffered no sequelae. He continued in the trial.

Patients # 005-114 and 006-312 experienced atrial fibrillation. The investigator believed that in both patients relationship to study drug was "possible." Patient 005-114 had taken his last dose of study medication 8 days before going to the emergency room where he complained of lightheadedness and shortness of breath. He was cardioverted. Patient 006-312 withdrew from the study because of "insufficient therapeutic effect" on November 14, 2000. He experienced atrial fibrillation on Novmeber 29, 2000, 22 days after his last intake of study drug.

Patient # 006-479 experienced "silent ischemia" on an EKG. Relationship to study drug was rated "unlikely."

Patient #018-646 experienced an arrhythmia. Relationship to study drug was rated as "unlikely." This patient with a previous history of coronary artery disease experienced atrial fibrillation on January 12, 2001. His last dose of 20 mg vardenafil was on December 4, 2000.

Patient # 003-1018 experienced polyarthralgia and polymyalgia. This event was rated as "probable." This 58-year-old man was taking allopurinol for gout. After taking his first dose of 20 mg vardenafil, he complained of polyarthralgia and polymyalgia. These same symptoms recurred after his second dose of study medication. CK values were normal at baseline but were not repeated during the event. His symptoms resolved.

In 3 patients with serious adverse events, the event was thought to be related to study drug by the investigator. Patient # 006-312 had atrial fibrillation, patient # 005-114 had atrial fibrillation and dizziness, and patient # 003-1018 had arthralgia and myalgia.

Three of the SAE's were cardiovascular events: Patient 006-312 (atrial fibrillation), patient 006-479 (myocardial ischemia), and patient 018-646 (arrhythmia which occurred more than 30 days after the last study drug intake).

G.6.3 Discontinuations due to adverse events:

Twenty-one patients (4%) discontinued because of an adverse event: headache (7), tachycardia (3), vasodilation (3), myalgia (3), rhinitis (2), dyspepsia (2), myocardial ischemia (1), palpitations (1), esophagitis (1), GGT increased (1), abnormal liver function tests (1), thrombocytopenia (1), arthralgia (1), dizziness (1), conjunctivitis (1), eye pain (1), and hematuria (1).

G.6.4 Frequent adverse events:

Drug related adverse events occurring in at least 5% of patients are shown in Table 1.

Table 1. Drug related adverse events occurring in at least 5% of patients.

Adverse event	Patients N=574
Headache – all Drug related	74 (13%) 41 (7%)
Vasodilation – all Drug related	52 (9%) 38 (7%)
Rhinitis – all Drug related	38 (7%) 16 (3%)
Dyspepsia – all Drug related	27 (5%) 11 (2%)
Accidental injury – all Drug related	20 (3%) 0 (0%)

G.6.5 Changes in laboratory values:

AST and ALT were increased in 9.8% and 12.5% of patients, respectively. Two patients had values > 3X ULN. Patient # 18-652 had a SGOT and SGPT of 140 and 105 U/L two days after last study drug intake. Patient # 02-1037 with cirrhosis had a SGOT and SGPT of 279 and 176 U/L at Visit 3. At Visit 5, 44 days after the last dose of vardenafil, he had normal SGOT and SGPT (21 and 22 U/L, respectively).

Nineteen patients (3.3%) had CK values exceeding 3X ULN. Two patients had CK's over 10X ULN.

Patient 007-511 had a CK of 313 at baseline which rose to 2552 U/L at Day 80. CK-MB was 6.3 (ULN=5.0. The initial abnormal values was also associated with

an elevated SGOT of 39 (ULN=36) and SGPT of 70 (ULN=43). At visit 6 (Day 175), CK was 236.

Patient 004-524 had a CK of 2339 U/L three days after the last study drug intake at Visit 6. CK-MB was not performed. CK was 184 U/L at baseline. He had no symptoms, no other abnormal laboratory tests, and the event was assessed as not clinically significant by the investigator.

G.7 Reviewer's assessment of safety: Although cardiovascular adverse events did occur, these were in general not temporally related to intake of study drug. This reviewer believes that Trial 10152 supports the safety of vardenafil for the treatment of erectile dysfunction.

Appendix H – Trial 10373 ("Randomized, double-blind, placebo-controlled, 2-fold cross-over study to investigate the acute effects of a single oral dose of a 20 mg BAY 38-9456 tablet on sperm motility in healthy male subjects")

H.1 Objective: The study objective was to determine the acute effects of a single oral dose of 20 mg vardenafil on sperm motility in healthy men. On an individual basis, a decrease in sperm motility of >20% was considered clinically relevant.

H.2 Study design and conduct: Sixteen healthy men aged 24 to 43 were evaluated in this randomized, placebo-controlled, double-blind, cross-over trial. At screening/enrollment, semen analysis, concentration of vardenafil and M1, and hormonal studies were obtained. At screening, a normal semen analysis (by WHO criteria) was required. On the day of the study, 20 mg vardenafil (or placebo) was administered and at 90 minutes post-dosing a semen analysis and semen for vardenafil and M1 concentration was obtained. Samples for PK analysis were obtained at baseline, 60 minutes, and 120 minutes. Treatment (vardenafil and placebo) were separated by at least 5 days.

The primary endpoint was sperm motility. A decrease in sperm motility WHO grade (A+B) of >20% was considered clinically relevant. Secondary objectives included the assessment of sperm count, sperm density, sperm morphology, and sperm viability. In addition, alpha-glucosidase and fructose were measured in the ejaculate. In serum, FSH, LH, testosterone, prolactin, DHEA-S, amd SHBG were determined. The concentration of BAY 38-7268 (free base of BAY 38-9456 and BAY 44-5576 in the ejaculate were measured and compared with the corresponding plasma concentrations. Vital signs were monitored. Semen analysis was repeated 1 to 2 weeks later if abnormalities were seen on the semen analysis post dosing of vardenafil. EKG was performed at baseline and at day 5 and 1-2 weeks post-dosing. A final semen analysis was performed about 74 days after treatment in the second study period.

H.3 Inclusion-exclusion criteria: Inclusion criteria included: 1) a normal semen analyses defined by WHO criteria – sperm concentration > 20 million/ml, sperm motility >50% (%sperm with WHO grade A+B motility) or >25% WHO grade A motility within 60 minutes of ejaculation, and sperm morphology >15% normal forms. Exclusion criteria included: 1) evidence on physical examination of of hypogonadism or testes measuring less than 12 cc using ultrasound 2) resting heart rate <45/min or > 90/min 3) Systolic blood pressure <100 mmHg or > 160 mmHg. 3) QTc interval > 450 msec.

H.4 Analysis of primary and secondary endpoints (pharmacodynamic data):

Only one patient had a semen analysis performed at the final examination (Day 74).

The results of the primary "endpoint" (sperm motility) are shown in Table 1.

Table 1. Descriptive statistics for percent sperm with motility WHO grade A+B.

Treatment	Time point	N<50%	Arithmetic Mean	SD	Minimum
None (N=15)	Screening	2	59.9	9.3	
Placebo (N=15)	90 minutes	2	61.7	8.7	
Vardenafil 20 mg (N=15)	90 minutes	1	63.1	9.2	

No patient had a decrease in WHO grade A+B motility of >20%. One patient had a decrease in WHO grade A motility of >20% (patient # 14 had a decrease of 36.8%). No additional semen sample had to be analyzed at final examination because of a change in sperm motility WHO grade (A+B).

The descriptive statistics for sperm concentration (sperm X 10^6/mL) are shown in Table 2.

Table 2: Descriptive statistics for sperm concentration (sperm X 10^6/mL).

Treatment	Time point	N< 20 X 10^6/mL	Arithmetic mean	S.D.	Minimum
None	Screening	0	77.5	38.77	
Placebo	90 minutes	0	90.4	49.8	
Vardenafil 20 mg	90 minutes	0	89.4	52.2	

No patient had a sperm morphology (normal forms) <15%.

H.5 Pharmacokinetic data:

Plasma and semen concentrations of BAY 38-7268 (free base of BAY 38-9456) and the active metabolite BAY 44-5576 were measured. Results are shown in Table 3.

Table 3. BAY 38-7268 and BAY 44-5576 PK results in plasma and semen following a single oral dose of 20 mg BAY 38-9456 (N=15).

Analyte	Parameter	Result
BAY 38-7268	Geometric mean plasma concentration (1hour-2 hour)	17.2 ug/L
	Semen concentration (1.5 hours)	8.46 ug/L
	Semen amount	0.0375 ug
BAY 44-5576	Geometric mean plasma concentration (1 hour-2 hour)	4.66 ug/L
	Semen concentration (1.5 hours)	3.22 ug/L
	Semen amount	0.0148 ug

H.6 Safety:

There were no deaths or serious adverse events.

Two patients taking placebo and 9 taking vardenafil 20 mg experienced adverse events (headache, vasodilation, dry mouth, diarrhea, nausea, rash, ear pain, and facial pain). All of the adverse events were rated to be of "mild intensity." One patient had an elevation in ALT, but elevated values were noted at screening.

No alterations in serum levels of FSH, LH, testosterone, or prolactin were observed.

H.7 Reviewer's assessment of Trial 10373: This study demonstrates that one 20 mg dose of vardenafil does not significantly alter sperm motility on a semen analysis obtained 90 minutes after dosing. This study does not evaluate the effects of repeated dosing, longer time-frames, and on other semen parameters (sperm concentration also did not change but would not be expected to change in this very short term study).

Appendix 1 – Trial 100304 ("A randomized, double-blind, placebo-controlled, cross-over study to evaluate the potentiation of the blood pressure lowering effect of sublingual nitroglycerin in combination with PDE-5 inhibitor, BAY 38-9456, in healthy male subjects") (Trial began 12/6/2000 and ended 3/22/2001)

I.1 Objective: The evaluation of the pharmacodynamic (blood pressure and heart rate) interaction between vardenafil (10 mg) and nitroglycerin (0.4 mg) in healthy male subjects.

I.2 Study conduct and design: Eighteen healthy men (mean age 48 years – range 40 to 65 years) were enrolled in this randomized, double-blind, cross-over, multiple dose study which consisted of two periods each of 5 days. The crossover design allowed each patient to be studied for 5 days with vardenafil and for 5 days with placebo. Study drug (or placebo) was given on days 1, 3, 4, and 5. Nitroglycerin was given on Days 2, 3, 4, and 5 of both periods. The trial was designed so that, on four separate days, nitroglycerin was administered 24, 8, 4, and 1 hour following the administration of study drug (vardenafil 10 mg or placebo). Blood pressure and pulse were monitored frequently. The primary pharmacologic variable was the maximum decrease in seated systolic blood pressure following the NTG doses.

On days 1, 3, 4, and, 5, BP and pulse were recorded seated and after standing for 2 minutes prior to drug administration. On day 1, patients were seated and had BP and pulse measured at 15, 30, 45, 60. 90, and 120 minutes after the dose of double-blind study drug. On days 2, 3, 4, and 5, 15-20 minutes before the NTG dose, patients were seated for 3 minutes and BP and pulse measured and this was followed by standing BP and pulse measurements. Patients were again seated and beginning 6 minutes before the NTG dose, BP and pulse were measured every 2 minutes. BP and pulse were measured every 2 minutes with the patient in the seated position for 0 to 30 minutes after the NTG dose. After the 30 minute recordings, patients stood and the BP and pulse were obtained. Subsequently, patients had sitting and standing BP and pulse at 10-minute intervals from this point up to 60 minutes after the NTG dose. Sitting and standing BP and pulse measurements were then obtained at 1.5, 2, 3, 4, 5, and 6 hours after NTG. After completing the vital signs monitoring on Day 5 of the first period, patients were discharged to return in 1 week for the second period of the crossover study. Blood samples for BAY 38-9456 were drawn pre-dose on Day 1 and at 30, 60, 90, 120, and 180 minutes after the dose of study drug on Day 1 of both periods. Blood was also drawn for BAY 38-9456 levels approximately 60 minutes after each dose of NTG on Days 2, 3, 4, and 5.

The changes in seated SBP, DBP, and pulse were analyzed using ANOVA with terms for sequence, patient within sequence, period, and treatment. Change from baseline was determined for each variable with the baseline established from the mean of the four every-other-minute readings immediately prior to the NTG

dose. These analyses were performed under each of the four conditions being assessed: NTG given 24 hours, 8 hours, 4 hours, and 1 hour after a BAY 38-9456/placebo dose.

Additionally, the BP "response" rate was determined using a threshold of 25 mmHg (over 60 or 90 minutes) following NTG administration to define a "responder."

I.3 Inclusion and exclusion criteria: Inclusion criteria included: 1) Healthy men aged 40-70 years. Exclusion criteria included: 1) symptomatic postural hypotension 2) systolic supine blood pressure must be between 100 and 150 mmHg 2) supine diastolic blood pressure must be between 60 and 95 mmHg 3) pulse must be between 45 and 110 bpm 4) drugs including corticosteroids, azole anti-mycotics (except fluconazole), macrolides (except azithromycin), phenytoin, nifazodone, rifampin, ritonavir, indinavir, androgens, and immunosupressants 5) use of Viagra within 48 hours of dosing 6) use of grapefruit juice or products 7) serum creatinine > 2.0 mg/dL at screening 8) current intake of > 14 standard alcoholic drinks/week

I.4 Results: Systolic blood pressure, diastolic blood pressure and heart rate data for Day 5 of the study, with an interval of 1 hour between study drug and NTG administration, are shown in Tables 1, 2, and 3. The change in mean data refer to BP and heart rate area-under-the-curve data divided by the period of observation.

Table 1. Effect of vardenafil on the systolic blood pressure response to NTG (Day 5)

	Placebo (LS mean)	Vardenafil (LS mean)	Difference	90% CI
Maximum change in SBP (mmHg) in period 60-90 min	-20.9	-19.2	1.7	-1.5 to 4.8
Change in mean SBP (mmHg) in period 0-60 min	-8.2	-8.9	-0.6	-3.1 to 1.8

LS mean data from the analysis of variance of the systolic blood pressure from Days 2, 3, and 4 show similar results. The mean maximum decrease in systolic BP for the vardenafil group was 22.2 on day 2, 16.8 on Day 3, 20.5 on Day 4 and 19.2 on Day 5. The mean maximum decrease in the placebo group was 20.6 on Day 2, 17.2 on Day 3, 18.4 on Day 4, and 20.9 on Day 5.

Table 2. Effect of vardenafil on the diastolic blood pressure response to NTG (Day 5)

	Placebo LS mean	Vardenafil LS mean	Difference	90% CI
Maximum change in DBP (mmHg) in period 0-60 min	-17.9	-20.1	-2.1	-5.2 to 0.9
Change in mean DBP (mmHg) in period 0-60 min	-7.1	-8.0	-0.9	-2.7 to 0.9

The mean maximum change and mean change in diastolic blood pressure was similar on Days 2, 3, and 4 as compared to Day 5.

Table 3. Effect of vardenafil on heart rate response to NTG (Day 5)

	Placebo LS mean	Vardenafil LS mean	Difference	95% CI
Maximum change in HR (bpm) in period 0-60 min	15.6	13.9	-1.7	-4.3 to 0.9
Change in mean HR (bpm) in period 0-60 min	2.6	-0.2	-2.8	-4.7 to -0.9

The mean maximum change and mean change in heart rate was similar on Days 2, 3, and 4 as compared to Day 5.

The number (%) of patients with a decrease in systolic blood pressure of at least 25 mmHg on Day 5 is shown in Table 4.

Table 4. Number (%) of patients with a decrease in systolic blood pressure (sitting) of at least 25 mmHg on Day 5.

		Placebo (n=18)	Vardenafil (n=18)	p-value
Drop of at least 25 mmHg (0 to 60 min)	Yes No	8 (44.4%) 10 (55.6%)	4 (22.2%) 14 (77.8%)	0.1025
Drop of at least 25 mmHg (0 to 90 min)	Yes No	8 (44.4%) 10 (55.6%)	4 (22.2%) 14 (77.8%)	0.1025

The data from Days 2, 3, and 4 are similar.

The number (%) of patients with a decrease in diastolic blood pressure of at least 25 mmHg on Day 5 is shown in Table 5.

Table 5. Number (%) of patients with a decrease in diastolic blood pressure of at least 25 mHg on Day 5.

		Placebo (n=18)	Vardenafil (n=18)	p-value
Drop of at least 25 mmHg 0 to 60 min)	Yes No	1 (5.6%) 17 (94.4%)	5 (27.8%) 13 (72.2%)	0.1025
Drop of at least 25 mmHg (0 to 90 min)	Yes No	1 (5.6%) 17 (94.4%)	5 (27.8%) 13 (72.2%)	0.1025

On Days 2, 3, and, 4 the number of patients with a decrease in diastolic blood pressure of greater than 25 mmHg is nearly identical in the placebo and vardenafil treated groups.

PK data: In 10 of the 18 patients, C_{max} was achieved within 1 hour after dosing. The median T_{max} was 1 hour.

I.5 Safety:

Adverse events: Three adverse events were reported (all during the vardenafil phase of the study). None of the adverse events was considered serious. No patient reported symptoms related to hypotension (dizziness, syncope, etc.).

Patient #1006 reported flushing and anxiety about 1 hour after the last dose of vardenafil. The events rated "mild" and resolved in 40 minutes.

Patient # 1006 was noted by the EKG reader to have an intraventricular conduction defect which showed a right bundle branch block. An EKG recorded approximately 50 hours after the last administration of vardenafil showed a more prominent RBBB. A screening EKG performed approximately 2 years prior to the present study also revealed RBBB.

Patient #1030, a 42-year-old healthy man, reported insomnia, dehydration, atrial arrythmia and tachycardia 4 to 6 days after the final dose of vardenafil. All of these events were rated as "mild" and "short-lived." This patient also had elevated CK levels (with normal troponin levels) during these events. At screening, his CK was elevated at 543 U/L (normal range: 21-213). Six days later, just before randomization, a repeat CK level was 296 U/L (within the 3X ULN allowed for in the protocol). During the placebo period, CK levels were 333 and 382 U/L. During the vardenafil period, CK levels were 722 and 427 U/L on Day 4 and 24 hours after the last dose of vardenafil. Three days later he

returned for follow-up and a repeat CK was 2675 U/L with a CK-MB band of 21.4 ng/mL (absolute value normal range: 0-5 ng/mL). The CK-MB band was less than 1% of the total CK level. The next day, the investigator contacted the patient and told him to go to the emergency room for laboratory follow-up. The repeat CK was 822 U/L (normal range: 75-170 U/L). The CK-MB and troponin levels were within normal limits. The AST and ALT were elevated approximately 10% over normal limits. Over the next 3 days, the CK levels fell to 698 U/L , the troponin level remained normal, and the AST and ALT returned to within normal limits. When first seen in the emergency room, the patient was mildly tachycardic (with an otherwise normal EKG) and the physician thought this was secondary to "dehydration." He denied chest pain. Two days later, the patient was seen by the principal investigator. An EKG showed an "ectopic atrial rhythm" not seen on prior EKG's (this event occurred 6 days after the last dose of vardenafil). The investigator believed that the lack of temporal relationship made the relationship to study drug unlikely. Three days later the patient was seen by a cardiologist. The EKG showed normal sinus rhythm and no abnormalities. The cardiologist's report mentioned that the patient complained at that time of slight non-radiating chest "ache" with a dry cough and headache. The cardiologist suspected "the most likely explanation is some kind of myositis, which could be either viral or an "autoimmune problem." The cardiologist's impression was that this patient did not have a coronary event related to the "experimental medication." Further contact with the patient 3 months after these events revealed no sequelae related to the events. The events all resolved spontaneously and were considered by the investigator as not being related to study drug.

Reviewer's comment: This reviewer believes that the relationship to study drug can not be excluded.

Summary and conclusions:

1) The vardenafil dose used in this study was 10 mg. (The doses proposed by the sponsor are 5, 10, and 20 mg).
2) The study population was young, healthy men.
3) The effect of vardenafil on systolic and diastolic blood pressure in subjects given nitroglycerin appears to be small (in the range of 1 to 2 mmHg) and not clinically significant.

Appendix J – Drug-Drug Interaction with CYP 3A4 Inhibitors

1) **Ketoconazole** (" Randomized, non-blind, non-placebo-controlled, 2-fold cross-over study to investigate the influence of a pre- and co-administration of 200 mg ketoconazole on the safety, tolerability and pharmacokinetics of Bay 38-9456 after a single oral dose of 5 mg of BAY 38-9456 in comparison to a single oral dose of 20 mg BAY 38-9456 alone in 12 healthy, male subjects; the pre-treatment phase will be 3 days" – Protocol # 010229)

Study design: This trial was a non-blind, non-placebo controlled, cross-over study to investigate the effect of co-administration of ketoconazole on the safety and pharmacodynamic effects of vardenafil. Twelve healthy men with a mean age of 30.5 years (range 23-37 years) were enrolled. The trial consisted of 2 different treatments with a "wash-out" phase of one week between treatments. The two treatments were: 1) 20 mg single dose of vardenafil given on one treatment day and 2) 200 mg ketoconazole once daily given for 4 days plus one single dose of 5 mg vardenafil given on the fourth day. End points were the pharmacokinetics of vardenafil and its major metabolites and safety parameters consisting of vital signs, adverse events, clinical chemistry, and EKG. EKG's were performed at screening, baseline, and at 1, 4, 11, and 24 hours post-vardenafil dosing as well as at follow-up 1 to 2 weeks later. Exclusion criteria included patients with a QTC interval over 450 msec.

Study population: Twelve healthy men with a men age of 30.5 years were enrolled.

Adverse events: Ten adverse events were reported in 9 patients. All adverse events were rated by the investigator as "mild." In the 5 mg vardenafil + 200 mg ketoconazole group, 6 adverse events (3 headache, 1 abdominal pain, and 2 rhinitis) occurred in 5 patients. In the 20 vardenafil group, 3 adverse events (1 headache, 1 vasodilation, and 1 rhinitis occurred in 3 patients. One adverse event of rhinitis was reported during the ketoconazole "run-in" period.

Reviewer's comment: No clinically significant adverse events were reported.

Pharmacokinetic data: Pharmacokinetic data for the vardenafil free base are shown in Table 1.

Table 1. Pharmacokinetic parameters for vardenafil

Parameter	Unit	5 mg vardenafil + ketoconazole	20 mg vardenafil
AUC	mcg h/L	190	76
AUC_{norm}	G h/L	3171	319
C_{max}	Mcg/L	25.0	24.6
$C_{max,norm}$	G/L	418	103
t_{max}	Hours	1.75	0.75

Reviewer's comment: For vardenafil, the normalized AUC increased 10-fold and the normalized C_{max} increased 4-fold when co-administered with ketoconazole.

QT and QT_C data: The QT and QT_C data are shown in Tables 2 and 3.

Table 2. QT data

Treatment	Mean value at time (milliseconds)	Mean change from baseline
5 mg vardenafil plus ketoconazole		
screening (n=6)	396	
baseline (n=12)	377	
1 hour (n=12)	380	2
4 hours (n=12)	374	-3
11 hours (n=12)	368	-9
24 hours (n=12)	373	-4
follow-up (n=6)	384	4
20 mg vardenafil		
screening (n=6)	379	
baseline (n=12)	392	
1 hour (n=12)	393	2
4 hours (n=12)	383	-8
11 hours (n=12)	378	-14
24 hours (n=12)	389	-2
follow-up (n=6)	387	-9

The maximum change from baseline in the 5 mg vardenafil plus ketoconazole group was 15 milliseconds at 1 hour, 27 at 4 hours, 20 at 11 hours, 22 at 24 hours, and 35 at follow-up. The maximum change from baseline in the 20 mg vardenafil group was 26 at 1 hour, 18 at 4 hours, 20 at 11 hours, 42 at 24 hours, and 26 at follow-up.

Table 3. QT_C data.

Treatment	N	Mean value at time (milliseconds)	Change from baseline
5 mg vardenafil + ketoconazole			
screening	6	408	
baseline	12	371	
1 hour	12	385	14
4 hours	12	380	9
11 hours	12	377	7
24 hours	12	377	6
follow-up	6	380	8
20 mg vardenafil			
screening	6	370	
baseline	12	372	
1 hour	12	377	5
4 hours	12	379	7
11 hours	12	379	7
24 hours	12	368	-3
follow-up	6	377	3

The maximum change in QTc for the 5 mg vardenafil plus ketoconazole group was 59 at 1 hour, 62 for 4 hours, 32 for 11 hours, 32 for 24 hours, and 31 at follow-up. The maximum change for the 20 mg vardenafil group was 33 at 1 hour, 23 at 4 hours, 30 at 11 hours, 25 at 24 hours, and 32 at follow-up.

Reviewer's comments: The reviewer is not able to make a meaningful interpretation of the EKG results. The EKG's were computer read. The correction method utilized for the QTc is not specified. There is no placebo group. No statistical analysis is provided. A positive control drug was not utilized.

Summary: The sponsor believes that the data support the conclusion that "patients who are being treated with known strong inhibitors of CYP 3A4 should be started on a reduced dose of vardenafil." Because of the 10-fold increase in normalized AUC and the 4-fold increase in normalized C_{max}, the 5 mg dose appears to be the maximum dose that patients should take in combination with ketoconazole. Safety (particularly QT data) has not be adequately evaluated at exposures significantly greater than 20 mg vardenafil. This study used a relatively low dose of ketoconazole (200 mg/day).

2.) Erythromycin ("Randomized, non-blind, two-fold cross-over study to investigate the influence of a pre- and co-administration of erythromycin on the safety, tolerability and pharmacokinetics of a single dose oral administration of BAY 38-9456 in 12 healthy male subjects" - Protocol # 010104)

Study design: This trial was a non-blind, two-fold crossover study to investigate the influence of a pre- and co-administration of erythromycin on pharmacokinetics and safety of vardenafil. Twelve healthy men (ages 18 to 50) underwent 2 treatments: 1) 20 mg single dose of vardenafil given on 1 treatment day and 2) 500 mg erythromycin tid given for 4 days plus one single dose of 5 mg vardenafil given on the fourth day. Endpoints were vardenafil pharmacokinetic data as well as safety (vital signs, adverse events, clinical chemistry, and EKG data). EKG's were obtained at screening, baseline, and at 4, 10, and 24 hours after dosing. PK data was obtained for 24 hours. The treatment periods were separated by a one week "wash out."

Study population: The study population was 12 healthy men between the ages of 18 and 50.

Adverse events: Eleven adverse events occurred in 7 patients during treatment with vardenafil. Five adverse events occurred in patients taking vardenafil 20 mg alone. In this group, there were 4 cases of headache and one case of arthralgia. Two of the headaches were rated as "moderate" and the rest of the adverse events as mild. Six adverse events occurred in the 5 mg vardenafil plus erythromycin group: headache (2), rhinitis, sinusitis, conjunctivitis, and eye pain. One headache, rhinitis, and conjunctivitis were rate as "moderate" and the remainder of the adverse events in this group were rated as "mild." Six adverse events occurred in the erythromycin "run-in" group. There were no serious adverse events.

Pharmacokinetic data: Pharmacokinetic data for vardenafil are shown in Table 1.

Table 1. Pharmacokinetic data for vardenafil.

Parameter	20 mg vardenafil alone	5 mg vardenafil + erythromycin
AUC (ug h/L)	53.0	53.3
AUC_{norm} (10^{-3} kg h/L	204	821
C_{max} ug/L	16.6	12.9
$C_{max,norm}$ (10^{-3} kg/L	63.9	199
T_{max} (hours)	1.0	1.0

The concomitant intake of vardenafil and erythromycin increased the normalized AUC by 4-fold and the normalized C_{max} by 3.1-fold.

QT_C data: QTc data are shown in Table 2.

Table 2. QTc data

Treatment	N	Mean value at time (msec)	Change from baseline	Max change
20 mg vardenafil				
baseline	12	368		
1 hour	12	378	10	30
4 hours	12	369	0	29
12 hours	12	380	12	24
24 hours	12	367	-1	29
5 mg vardenafil plus erythro.				
Baseline	12	373		
1 hour	12	375	2	32
4 hours	12	372	-1	15
12 hours	12	384	11	37
24 hours	12	371	-2	22

In the vardenafil plus erythromycin group, one patient had an increase in QTc of 31 to 60 msec at one hour and one patient had an increase of QTc of 31 to 60 msec at 12 hours post dosing.

Reviewer's comments: The reviewer is not able to make a meaningful interpretation of the EKG results. The correction method utilized for the QTc is not specified. There is no placebo group. No statistical analysis is provided. A positive control drug was not utilized.

Summary: The sponsor believes that the data support the conclusion that "patients who are being treated with known inhibitors of CYP 3A4 should be started on a reduced dose of vardenafil." Because of the 4-fold increase in normalized ÅUC and the 3-fold increase in normalized C_{max}, this reviewer believes that erythromycin should not be given with the 20 mg vardenafil dose.

3.) Indinavir ("A study to evaluate the potential reciprocal pharmacokinetic interaction between indinavir (Crixivan) and vardenafil" – Protocol 100336)

Study design: This was an open label, non-randomized study to evaluate the PK of vardinafil alone and in combination with indinavir. Eighteen healthy men (12 Caucasian and 6 Black) between the ages of 18 and 45 were enrolled. The

vardenafil dose was 10 mg. A single dose of 10 mg vardenafil was given on day 1 and a single dose was given on Day10. Indinavir (800 mg tid – the standard dose) was given on Days 4 through 10. An EKG was performed on Day 11 approximately 24 hours after the last dose of vardenafil.

Adverse events: There were no serious adverse events. One patient discontinued because of rash while on indinavir alone. Headache occurred in one patient on Day 1 (vardenafil alone). Eight patients experienced headache on Day 10 (vardenafil and indinavir). On Day 10, adverse events consisted of dizziness (5), rhinitis (4), and dyspepsia (2). The only cardiovascular events were peripheral edema on Day 6 (n=1) and vasodilation (flushing) on Day 10 (n=1).

Pharmacokinetic data: The AUC and Cmax of vardenafil increased by approximately 16-fold and 7-fold, respectively, when co-administered with indinavir. Concentrations of the M1 metabolite were significantly reduced following treatment with indinavir. The AUC and Cmax of indinavir were reduced by 30 to 40% when vardinafil was co-administered.

EKG data: EKG's were performed greater than 24 hours after the last vardenafil dose. No placebo group was included. This reviewer does not believe that meaningful conclusions regarding the QTc data can be drawn.

Summary: The sponsor believes that vardenfil should be given "in the lowest available dose" to patients taking indinavir. Indinavir increased the Cmax by 7-fold and the AUC by 16-fold. This reviewer believes that indinavir (and other proteases which are potent CYP 3A4 inhibitors) should be contraindicated at the vardenafil 5, 10, and 20 mg doses because adequate safety information (including QT data) is not available at the high exposures which would result.

Appendix K – Alcohol Interaction ("Randomized, double-blind, placebo-controlled, 3-fold cross-over study to investigate the hemodynamic and pharmacokinetic interactions of a single oral dose of a 20 mg BAY 38-9456 tablet in healthy male subjects when given together with alcohol" - Protocol 10348)

Study design: This study was a randomized, double-blind, placebo controlled, 3-way cross-over study to investigate the hemodynamic and pharmacokinetic interactions of a single oral dose of 20 mg vardenafil with alcohol. Alcohol was administered as ethyl alcohol 0.5 g/kg body weight in 200 ml orange juice. The alcohol placebo used was 2 drops of ethyl alcohol added to 200 ml orange juice. Twelve healthy men (median age 37.5 years) were randomized.

There were 3 treatment periods of 1 day each, separated by at least a 1-week wash-out period. The 3 treatment groups were: 1) 20 mg vardenafil and 0.5 g ethanol/kg 2) vardenafil placebo and 0.5 g ethanol/kg and 3) 20 mg vardenafil and ethanol placebo. Hemodynamic events were assessed using the maximal decrease from baseline until 4 hours after administration. Supine diastolic blood pressure was the primary parameter. Blood pressure and pulse were taken. Adverse events, blood pressure, heart rate, EKG, and laboratory parameters were assessed and the PK of vardenafil and alcohol were analyzed.

Study population: Twelve healthy men aged 26 to 43 years (median 37.5) were enrolled.

Adverse events: There were no serious adverse events. Overall, adverse events occurred in 10 patients in the vardenafil plus ethanol group, 5 in the ethanol alone group, and 9 in the vardenafil alone group.

In the vardenafil and ethanol group, the following adverse events were reported: injection site edema (2), face edema (swelling around the eyes) (1), headache (3), vasodilation (7), diarrhea (1), nausea (1), thinking abnormal (1), and rhinitis (7). All of the events were rated as "mild" except for one headache which was rated as "moderate."

Reviewer's comment: The reviewer does not understand the nature of "injection site edema."

In the ethanol alone (vardenafil placebo) group, the following adverse events were reported: vasodilatation (3), thinking abnormal (1), rhinitis (2), and sweating (1). All the adverse events were rated as "mild."

In the vardenafil alone (ethanol placebo) group, the following adverse events were reported: headache (2), vasodilatation (5), diarrhea (1), rhinitis (4), and lacrimation disorder (1). All of the adverse events were rated as "mild."

Hemodynamic data:

The maximum heart rate differences are shown in Table 1.

Table 1. Maximum heart rate differences between groups

Treatment	Difference (95% confidence intervals)
20 mg vardenafil +ethanol active – vardenafil placebo + ethanol active	3.4 (-2.24 - -9.07
20 mg vardenafil + ethanol active – 20 mg vardenafil + ethanol placebo	11.5 (5.85 – 17.16)
Vardenafil placebo + ethanol active – 20 vardenafil + ethanol placebo	8.08 (2.43 – 13.74)

The most prominent increase with single drug administration was seen with ethanol (20 bpm). When both drugs were administered concomitantly, mean maximum heart rate increased by 23 bpm. A secondary statistical analysis revealed a significant difference in the increase of maximum heart rate comparing vardenafil + ethanol with vardenafil alone (point estimate of difference 11.5 bpm. There is also a significant difference comparing ethanol alone with vardenafil alone (8.08 bpm).

The maximum systolic blood pressure differences between the groups is shown in Table 2.

Table 2. Maximum systolic blood pressure differences between treatment groups (mmHg)

Treatment	Difference (95% confidence intervals)
Vardenafil + ethanol active – Vardenafil placebo + ethanol active	2.67 (-3.3 –8.68)
Vardenafil + ethanol active – Vardenafil + ethanol placebo	1.0 (-5.01-7.01)
Vardenafil placebo + ethanol active – Vardenafil + ethanol placebo	-1.67 (-7.68 – 4.34)

The most prominent decrease with a single drug administration was seen with ethanol (5.9 mmHg). When both drugs were administered concomitantly, mean maximum systolic blood pressure decreased by 6.3 mmHg. The secondary statistical analysis revealed no significant difference in the decrease of maximum systolic blood pressure when comparing the various treatments.

The most prominent decrease in maximum mean diastolic blood pressure with a single drug administration was seen with ethanol (7.5 mmHg decrease).

When both drugs were administered concomitantly, mean maximum systolic blood pressure decreased by 9.8 mmHg.

Pharmacokinetic data: There was no significant difference in Cmax and AUC of vardenafil when administered with either ethanol or ethanol placebo.

The Cmax of ethanol was approximately 730 ug/L in both the vardenafil and the vardenafil placebo groups.

Reviewer's comment: The Cmax for ethanol was near the "legal limit."

Summary and conclusion: The addition of 20 mg vardenafil to ethanol ingestion raising the Cmax of ethanol to near the "legal limit" does have a small effect on heart rate (an increase of approximately 3 bpm) and blood pressure (a decrease of approximately 1-2 mmHg in systolic and diastolic blood pressure) over that seen with ethanol alone. These changes are not clinically significant. No significant adverse events were reported.

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Appendix L– Cardiovascular response to exercise in patients with coronary artery disease. Two studies (#'s **100408 and 100302**) are reviewed.

"A randomized, double-blind, placebo-controlled, crossover study to evaluate the effect to the PDE5 inhibitor, BAY 38-9456 20 mg, on the cardiovascular responses to exercise in patients with coronary artery disease" – Protocol 100408.

(An interim report covering the first 14 patients who were randomized and who completed Study 100408 as of December 28, 2001, was submitted to the FDA as part of the 4-month safety update. This final report covers all randomized/completed patients and includes results and analyses for all safety and pharmacodynamic parameters. The results of the pharmacokinetic analyses are not included, as the assay of vardenafil plasma levels is ongoing. The PK results will be submitted at a later date.)

L.1. Objective:
The primary objective of this study is to evaluate the effect of 20 mg vardenafil versus placebo on total treadmill exercise time in patients with stable exertional CAD. Secondary objectives are: 1) to evaluate the effect of vardenafil 20 mg versus placebo on the time to the onset of angina pectoris/angina equivalent and 2) the time to the onset of exercise induced ST-segment depression greater than or equal to 1 mm horizontal or down-sloping from baseline, or greater than or equal to 2 mm slowly up-sloping from baselilne.

L.2 Study design: This was a randomized, placebo-controlled, double-blind, crossover, single dose, multicenter study comparing the effect of 20 mg vardenafil and placebo on the total treadmill exercise time in patients with stable exertional CAD. Thirty-nine patients were randomized. Patients had qualification treadmill tests (ETT) at Visits 1 and 2. Patients must have been able to exercise at least 3 minutes using a standatd Bruce ETT protocol at both visits. They must have ended the ETT within 10 minutes and demonstrated one of the following conditions: 1) angina pectoris or angina equivalent (pain intensity of at least 7 on a scale of 1 to 10) 2) in the absence of angina/angina equivalent or angina rated less than 7, the patient's reason for terminating exercise should be because of other symptoms (eg shortness of breath or fatigue) associated with exercise induced ST-segment depression >1 mm horizontal or down-sloping change from baseline or >2 mm slowly up-sloping change from baseline at 0.06-0.08 seconds after the J-point, using PR segment as baseline. If the patient discontinued the ETT because of an adverse event (eg hypotension), the patient was not randomized. To qualify, a patient's total exercise times on the treadmill at Visits 1 and 2 must have been within 15% of each other. If the first 2 ETT's did not agree within 15%

of each other, patients were allowed to return one week later for a third qualifying ETT. The optional third ETT (Visit 2.1) must have agreed to within 15% of the second ETT to qualify for entry into the double-blind phase of the study. During the double-blind treatment phase (Visits 3 and 4), each patient received 20 mg vardenafil and placebo, one-week apart in a randomized, 2-way crossover study design.

Patients must have been withdrawn from immediate-release sublingual nitrates for 24 hours before the start of an ETT and could not resume taking sublingual nitrates for 24 hours after completing the ETT. Patients were withdrawn from all other nitrate preparation 1 week before Visit 1 and could not resume taking slow-release nitrates until completion of the study (24 hours after the final dose at Visit 4). Patients taking beta-blockers, cardizem, and verapamil were to hold their dose on the mornings of each ETT until after completion of the treadmill test. The treadmill test was initiated one hour after vardenafil/placebo dosing.

The EKG was monitored continuously during the test through at least 3 leads (2 chest and 1 limb lead) and a 12-lead EKG was recorded every minute during the test. BP and heart rate were monitored. EKG tracings were examined continuously during the ETT for ST-segment depression >1 mm from baseline level. During the single-blind potion of the study (Visits 1, 2, and 2.1), patients received a single dose of placebo at each visit. The sponsor believes that a minimum of 3 minutesof a Bruce ETT protocol is equivalent to a level of exercise that is considered average for sexual intercourse, that is 3 to 5 metabolic equivalents. The logarithm of the time to termination of exercise (seconds) was analyzed using analysis of variance (ANCOVA) with terms for sequence, patient within sequence, period, and treatment. A 1-sided test procedure with non-inferiority limit of 0.85 and significance level of 5% was used to determine non-inferiority.

Population and inclusion criteria: Patients were men aged 40 to 80 years with documented stable exertional coronary artery disease documented by at least one of the following: 1) prior history (not within 6 months) of MI, CABG, PTCA, or stenting 2) positive coronary angiogram showing at least 60% narrowing of the diameter of at least one major coronary artery and 3) stress echocardiogram or stress nuclear perfusion study.

Results:

The exercise treadmill time for all patients valid per-protocol is shown in Table 1.

Table 1. Exercise treadmill completion times, all patients valid per protocol (seconds +/- standard deviation). (N=36)

Parameter	Vardenafil 20 mg	Placebo
Total treadmill exercise time	413.5 +/- 114	410.7 +/- 124
Total time to angina pectoris	354.2 +/- 137	346.7 +/- 143
Total time to ST-segment depression 1 mm or greater change from baseline	364.3 +/- 101	366.2 +/- 105

The statistical analysis of the primary outcome variable, total treadmill exercise time, and the 2 secondary variables, total time to angina and total time to 1 mm or greater ST-segment depression is shown in Table 2.

Table 2. Analysis of exercise treadmill completion times, all patients valid per protocol.

Parameter	Ratio of LS means (vardenafil/placebo)	p-value ratio = 1
Total treadmill exercise time (N=36)	1.015	0.4360
Total time to angina pectoris (N=36)	1.024	0.3742
Total time to ST-segment depression (N= 36 vardenafil; 25 placebo)	0.998	0.9698

The data for patients with **both** angina and 1 mm or greater ST-segment depression at Visits 3 and 4 are shown in Table 3. The statistical analyses are shown in Table 4.

Table 3. Exercise treadmill completion times, all patients with both angina and 1 mm or greater ST-segment depression (**mean seconds** +/- standard deviation).

Parameter	20 mg vardenafil	Placebo
Total treadmill exercise time (N=10)	406.6 +/- 105	389.9 +/- 122
Total time to angina pectoris (N=10)	331.0 +/- 103	310.0 +/- 108
Total time to ST-segment depression (n=10)	372.4 +/-124	345.0 +/- 119

Table 4. Analysis of exercise treadmill completion times, all patients with angina and 1 mm or greater ST-segment depression.

Parameter	Ratio of LS means (vardenafil/placebo)	p-value for ratio = 1
Total treadmill time (N=10)	1.067	0.1096
Total time to angina pectoris (N=10)	1.071	0.0725
Total time to ST-segment depression	1.087	0.3650

In this group of patients, a two-sided test of the ratio of geometric mean being different from one was non-significant, and one-sided tests of the ratio of geometric means being less than 0.85 were rejected in all cases, indicating non-inferior effect of vardenafil treatment.

Two patients (#'s 8001 and 8002) were inadvertently dosed with 40 mg (2 tablets). Pharmacodynamic data are shown in Table 5.

Table 5. Exercise treadmill completion times for 2 patients dosed with 40 mg (mean in seconds).

Patient	Parameter	40 mg vardenafil	Placebo
8001	Total treadmill exercise time	310	314
	Total time to angina pectoris	300	280
	Total time to ST-segment depression	310	300
8002	Total treadmill exercise time	204	219
	Total time to angina pectoris	175	77
	Total time to ST-segment depression	175	120

Reviewer's comment: The mean total treadmill time (the primary efficacy endpoint) was slightly increased for the vardenafil compared with the placebo group. This difference was not statistically significant. There was no statistically significant difference between the vardenafil and placebo groups with respect to mean total time to angina and in mean total time to ST-segment depression.

Adverse events:

Deaths: No deaths were reported.

Significant adverse events:

Two serious adverse events occurred during the single-blind placebo ETT qualification phase of the study. These events were vasovagal syncope and transient monocular blindness and carotid artery stenosis.

One patient (#7002) discontinued the study because of a medically important adverse event. This 72-year-old man experienced severe hypotension and dizziness beginning at the termination of the first ETT following a vardinafil 20 mg dose. Just before starting the ETT, a pre-exercise standing blood pressure was 90/60 mmHg and the heart rate was 89. The pre-dose BP was 128/74 and the heart rate was 60 bpm. The hypotension and dizziness lasted for 75 minutes. Beginning about 20 minutes after the ETT, his BP dropped to 75/0 mmHg. His heart rate was 126 bpm. He was unable to stand because of the dizziness. He was treated with oral fluids. Heart rate was stable at 60-70 bpm and the EKG was unremarkable. He was not hospitalized and went home approximately 2 ½ hours after completing the treadmill test. He had fasted for 12 hours prior to the ETT and the sponsor believes that hypovolemia may have been a factor in the occurrence of hypotension. Medications included amlodipine and digoxin; dosing of both medications was delayed after completion of the ETT. He had discontinued Imdur slow-release nitrate approximately 30 days before the start of the study. The patient had experienced a prior episode of hypotension after taking 2 sublingual nitrate tablets several years before enrolling in the study. Follow-up at 7 days revealed no sequelae.

Adverse events were reported in the vardenafil period at more than twice the incidence as was seen during the placebo period. The most common adverse events were flushing (21%), dizziness (13% - compared to 5% in the placebo group), and rhinitis (5%). Five of the 7 patients who reported dizziness were in the vardenafil group. In 4 of the 5 cases the dizziness was rated as "mild." The fifth case of dizziness was patient #7002 and this patient is discussed above.

Vital signs: There was a greater drop in systolic blood pressure in the post-exercise period after vardenafil treatment with mean changes from baseline at time points during exercise ranging from –1.4 to –6.7 mmHg for vardenafil compared with –0.9 to –2.3 for placebo. Outlier analysis showed no difference in the number of patients with clinically significant change in systolic or diastolic BP during exercise, while during recovery, there were two patients who had systolic BP <90 mmHg and reduction >20 mmHg after vardenafil, compared to none after placebo. Neither patients experienced dizziness. Both patients were on at least 2 anti-hypertensive medications.

EKG:

After correcting for heart rate with the Fridericia formula, the mean change from the Visit 2 baseline QTc was 10.2 msec in the vardenafil group and 6.9 msec in the placebo group.

"A randomized, double-blind, placebo-controlled, crossover study to evaluate the effect of the PDE5 inhibitor, BAY 38-9456, on the cardiovascular responses to exercise in patients with coronary artery disease" – Protocol 100302.

Trial 100302 was nearly identical to trial 100408. The dose of vardenafil in 100302 was 10 mg instead of 20 mg and patient age for inclusion was 40 to 70 instead of 40 to 80 years. Otherwise, the design, inclusion criteria, and primary and secondary endpoints of the two studies were identical. Forty-one patients were randomized.

Results:

The results of the primary endpoint (total treadmill exercise time) and the secondary endpoints (total time to angina pectoris and total time to ST-segment depression are shown in Table 1.

Table 1. Exercise treadmill completion times, all patients valid per-protocol (mean in seconds +/- standard deviation).

Parameter	Vardenafil 10 mg	Placebo
Total treadmill exercise time (N=39)	433 +/- 109	427 +/- 105
Total time to angina pectoris (N=34)	291 +/- 123	292 +/- 110
Total time to ST-segment depression (N=31)	381 +/- 108	334 +/ 108

The data in patients with angina and 1 mm or greater ST-segment depression also did not show any significant differences between the vardenafil and placebo groups. For patients with 1 mm or greater ST-segment depression, vardenafil improved by 15% the patient's time to the appearance of 1 mm or greater ST-segment depression.

Pharmacokinetic data: The mean plasma vardenafil level at 90 minutes after dosing was 7.9 ng/ml (N=39). This plasma level is consistent with the vardenafil plasma levels at this time point in prior studies and is near the expected C_{max}.

Adverse events:

Deaths: There were no study deaths.

Serious adverse events: One patient developed sepsis 4 days after the final dose of study drug (vardenafil). The sepsis was the result of chelation therapy

performed in Canada. The patient was hospitalized, treated with antibiotics, and made a complete recovery.

Reviewer's comment: The reviewer does not think that the serious adverse event was related to study drug.

Frequent adverse events: The 2 most frequent adverse events in the vardenafil groupwere vasodilation (12%) and headache (7%). Two patients reported dizziness (1 in the placebo and 1 in the vardenafil group). Both cases of dizziness were rated as "mild."

EKG: In patient #8006, a QTc value of 505 msec was measured during Visit 4 (10 mg vardenafil). The patient's heart rate was 106 bpm compared with 87 bpm at Visit 3. The Fridericia's correction was 459 msec compared to 430 msec at the prior visit.

Reviewer's comment: The significance of the prolonged QTc in this one patient is not clear to this reviewer.

Conclusions: Trials 100408 and 100302 do not demonstrate any adverse effects of vardenafil (either 10 or 20 mg) on total treadmill exercise time, time to angina pectoris, or time to ST-segment depression during treadmill testing in patients with stable coronary artery disease.