Reviewer's comments:

1) *Vardenafil doses of 5, 10, and 20 mg are clinically and statistically superior to placebo.*
2) *In 3 of the 4 major trials, the dose of 20 mg is not clinically or statistically superior to 10 mg. In Trial 100250 (diabetic patients with erectile dysfunction), the difference between 20 and 10 mg for the EF domain of the IIEF was statistically different in favor of the 20 mg dose. In this same Trial the data for SEP 2 and SEP 3 were marginally numerically superior for the 20 mg dose but the differences did not reach statistical significance. None of the "pivotal" studies was designed to specifically compare the 10 and 20 mg doses of vardenafil.*
3) *All 4 studies enrolled large numbers of patients (70%, 59%, 60%, and 80%) who had previously taken sildenafil. Erections had been improved by sildenafil in nearly all of these patients. A "history of unresponsiveness to sildenafil" was an exclusion criterion in Trials 100249, 100250, and 100285. A history of significant side effects with sildenafil use was an exclusion criterion in Trials 100250 and 100285. It is difficult to enroll large numbers of patients in erectile dysfunction trials who are naïve to sildenafil. This reviewer believes that the data presented in this NDA provides sufficient evidence to approve vardenafil at doses of 5, 10, and 20 mg from an efficacy standpoint. Despite the exclusion of patients with a history of "significant side effects with sildenafil use in Trials 100250 and 100285," this reviewer believes that there remains a safety data base which is adequate for evaluation.*
4) *There is insufficient efficacy data directly comparing vardenafil to other drugs indicated for the treatment of erectile dysfunction to make meaningful comparisons.*

With regard to the low end of the dose ranging studies, the sponsor also submitted the results of Phase 3 study 10232. Trial 10232 included the same patient population and same primary endpoints as the 4 major efficacy studies but evaluated doses of vardenafil of 2.5 and 5 mg. The efficacy results from Trial 10232 are shown in Table 7.

Table 4-30: Study 10232—Results[a] IIEF EF Domain at Week 12 LOCF and Overall Per-patient Diary Results for Penetration and Maintenance of Erection[a] (ITT Population)

	Placebo	Vardenafil 2.5 mg	Vardenafil 5 mg
IIEF domain: erectile function at LOCF			
N	157	160	163
LS mean baseline	13.61	12.92	13.53
LS mean value±SE at LOCF	15.10±0.70	18.79±0.69	20.31±0.65
		P<0.0001	P<0.0001
Overall per-patient diary: success in penetration (% yes)			
N	164	169	167
LS mean baseline	51.57	53.30	46.88
LS mean value±SE at LOCF	54.74±2.78	65.87±2.68	76.26±2.60
		P = 0.0008	P<0.0001
Overall per-patient diary: maintenance of erection for successful intercourse (% yes)			
N	163	169	167
LS mean baseline	18.57	16.83	16.61
LS mean value±SE at LOCF	28.66±3.07	47.35±2.95	59.02±2.86
		P<0.0001	P<0.0001

Source: Tables 14.2/1.1 and 14.2/1.2, Study 10232

[a] The *P* value is for the comparison of the vardenafil groups with placebo

Reviewer's comment: Both the 2.5 and 5 mg doses of vardenafil were statistically significantly more effective than placebo in terms of all 3 primary endpoints. Vardenafil 5 mg was statistically significantly better than the 2.5 mg dose with respect to penetration and maintenance of erection. The sponsor believed that the increases measured by the primary endpoints with the 2.5 mg dose were not clinically meaningful and since the the 2.5 mg dose had a lack of an obvious safety advantage over the 5 mg dose, the development of the 2.5 mg dose was not pursued.

6.4 Efficacy conclusions:

In the opinion of this reviewer, adequate and well-controlled studies have demonstrated that the 5, 10, and 20 mg doses of vardenafil are clinically and statistically effective in the treatment of erectile dysfunction.

7. Integrated Review of Safety:

7.1 Brief Statement of Findings:

In the opinion of this reviewer, there are 2 over-riding safety concerns.

1) This reviewer is unable to exclude an effect of vardenafil on the QT interval. A CardioRenal consultation was obtained and the conclusion of the consultant was that "although the available data raise no concern regarding arrhythmogenic potential, the data are not particularly conpelling that such a risk has been ruled out."

2) The nitrate interaction study included a 10 mg, but not a 20 mg dose, of vardenafil. This is an approvability issue for the 20 mg dose.

In addition to 1) and 2) above, the etiology of back pain needs to be addressed. The etiology of back pain seen with vardenafil exposure is unknown. This adverse event appears to a "drug class effect" of PDE5 inhibitors. The back pain subsides within 48 hours of discontinuing the drug. There is no associated significant CK increase. In the Phase 3 clinical trials, the incidence of back pain was not different from placebo. In the opinion of this reviewer, the etiology of back pain seen with vardenafil should be further evaluated (by Phase 4 commitment) but is not an approvability issue.

7.2 Materials Utilized in the Review:

The ISS (see Appendix E), 4 month safety update, and 7 month safety update were reviewed.

Safety data from the following trials were reviewed in detail:

Four primary efficacy trials:
100249 (general erectile dysfunction population) (see Appendix A)
10128 (general erectile dysfunction population) (see Appendix B)
100250 (erectile dysfunction in diabetics) (see Appendix C)
100285 (erectile dysfunction following radical prostatectomy (See Appendix D)

10125 (12 month safety study) (see Appendix F)
10152 (6 month safety extension of Phase 2b study 100199) (see Appendix G)

10373 (sperm motility study) (see Appendix H)
10304 (nitroglycerin interaction study) (see Appendix I)

10229, 10104, and 10336 (ketoconazole, erythromycin, and indinavir interaction studies) (see Appendix J)

10348 (alcohol interaction study) (see Appendix K)

94, 10006, 10104,10229, 10010, 10011, 100195, and 100196 (QT studies) (see Appendix M)

100408 and 100302 (cardiovascular response to exercise) (see Appendix L)

Other trials were reviewed in less depth and not included in the appendices:

10194 (extension of Trial 10194)
10197 (visual safety trial)
10047 (PK study at 40 mg dose)
10232 (Phase 3 trial of 2.5 and 5 mg doses)
10312 (extension of 100250)

The four month safety update was submitted on January 23, 2002. This update included: 1) a clinical safety update report, the final study report for Trial 10125 (12 month study of 10 and 20 mg vardenafil), the final study report for Trial 10152 (6 month study of 20 mg vardenafil), the final study report for study 100396 (study of the effect of 10 mg dose of vardenafil on aspirin induced bleeding time), and an interim study report of Trial 100408 (effect of 20 mg vardenafil on cardiovascular response to exercise in patients with coronary artery disease). Trials 10125 and 10152 are separately reviewed in appendices F and G. The 7 month safety update was submitted on April 23, 2002. This update included: 1) clinical safety update report 2) interim report of complete pharmacodynamic and safety data for all enrolled patients treated with 20 mg vardenafil dose in Trial 100408

Vardenafil is not approved in other countries and post-marketing data is not available.

7.3 Patient Exposure

Overall, vardenafil was administered to 3750 patients during the clinical trials. Approximately 1630 patients have been treated for 6 months or longer and 730 patients have been treated for at least one year. 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 Trials 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).

7.4 Safety Findings in Clinical Studies

Deaths:

Seven patients enrolled in clinical trials died.

In placebo-controlled trials, one death occurred in a placebo group, one in a drug comparator (sildenafil) group, and one in a 2.5 mg vardenafil group. The patient in the 2.5 mg vardenafil group (Patient #10232-013-004) was a 55-year-old man with diabetes and hypercholesterolemia who experienced a myocardial infarction 6 days after taking his last dose of study drug. (The case report form was reviewed. Last diary entry for medication use was 6 days before myocardial infarction). He underwent coronary artery bypass surgery, developed pneumonia, experienced acalculous cholangitis, and died 51 days after the myocardial infarction. The investigator did not consider the event to be related to vardenafil.

Three deaths occurred in uncontrolled and ongoing studies. One 67-year-old man (Patient #100312-905-004) with a history of coronary artery disease and hypertension died suddenly 1 month after entering an extension study and 21 days after his last dose of 10 mg vardenafil. (His wife returned the diary and unused medication to the site. Review of the case report form shows diary data of last study drug being taken 21 days before death. All unused medication returned and none missing). He had been taking nitroglycerin more frequently in the weeks before his death due to worsening chest pain. This fact was never revealed to the study site by the patient. One patient committed suicide and one died of lung cancer prior to taking any study drug.

The seventh death was a 69-year-old man (Patient # 10125-110-342) who died in his sleep and was found unresponsive at home. An autopsy determined the cause of death to be "cardiovascular disease secondary to diabetes and hypertension." "No other information is available." This reviewer is unable to locate data

relating to diary information and medication use just prior to the patient's death in the case report form.

Serious adverse events: The incidence of specific serious adverse events was similar in the vardenafil and placebo groups and no single event deemed "serious" was associated more often with drug than with placebo.

The incidence rates for serious adverse events in Safety Pool 3 (all placebo controlled studies using 5, 10, or 20 mg vardenafil doses – Trials 100249, 10128, 100250, 100285, and 10232) are shown in Table 8.

Table 8.

Table 7-30 Pool 3: Incidence Rates of Serious Treatment Emergent Adverse Events by Treatment (Events Occurring in at Least 2 Patients in a Treatment Group

Adverse Event	Placebo n=793	Vardenafil n=1812
Any Event	26 (3.3%)	49 (2.7%)
Accidental Injury	3 (0.4%)	5 (0.3%)
Hernia	3 (0.4%)	3 (0.2%)
Hyperglycemia	0 (0.0%)	3 (0.2%)
Chest Pain	3 (0.4%)	2 (0.1%)
Atrial Fibrillation	1 (0.1%)	2 (0.1%)
Syncope	1 (0.1%)	2 (0.1%)
Cholelithiasis	0 (0.0%)	2 (0.1%)
Abnormal Liver Function Tests	0 (0.0%)	2 (0.1%)
Diabetes Mellitus	3 (0.4%)	1 (<.1%)
Urogenital Surgery	2 (0.3%)	0 (0.0%)

Pool 3, Table 2/1.11

Those serious adverse events in vardenafil patients assessed as probably or possibly related to treatment as assessed by the investigator (Pool 4 – all controlled and uncontrolled Phase 3 studies using doses of 5, 10, or 20 mg of vardenafil) are shown in Table 9.

Table 9.

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Table 7-32 Pool 4: Treatment-Emergent Serious Adverse Events in Vardenafil Patients Assessed as Probably or Possibly Related to Treatment

Adverse Event	Relationship		Patient Number
	Possible	Probable	
Asthenia	X		10152-05-0114
Malaise	X		10152-05-0114
Chest tightness		X	100250-047-005
Atrial fibrillation	X		10152-05-0114
	X		10152-06-0312
	X		100249-013-016
ST Depression	X		100250-017-009
Cerebrovascular accident	X		100312-028-014
	X		100312-028-040
Syncope	X		100249-044-057
Abnormal liver function tests	X		10232-004-0030
Gastritis	X		10125-38-002
Amnesia	X		100250-043-005
Dizziness	X		10152-05-0114
Hypesthesia	X		100250-904-008
Asthma		X	100250-047-005
Dyspnea	X		10152-05-0114
		X	100250-047-005
Larynx edema		X	100250-047-005

Pool 4, Table 2/1.22

Five of these events (asthenia, malaise, atrial fibrillation, dizziness, and dyspnea) occurred simulataneously in one patient (10152-05-0114). This 64-year-old man with a history of diabetes, hypercholesterolemia, and hypertension developed rapid atrial fibrillation 8 days after his last dose of 20 mg vardenafil. Another case of atrial fibrillation (100249-013-016) occurred in a 68-year-old man with a history of angina, COPD, and heartburn who was discovered at his last clinic visit to have developed atrial fibrillation. His last dose of 10 mg vardenafil was taken one day earlier. A third case of atrial fibrillation (10152-06-0312) occurred 22 days after last study drug intake.

Four of these events (chest pain, asthma, dyspnea, and larynx edema) occurred simultaneously in a 59-year-old man (100250-047-005) with a history of obesity, sleep apnea, seasonal allergies, hypertension, coronary artery disease, COPD, cardiomegaly, edema, and hypothyroidism. He developed chest tightness, wheezing, a sense of throat closing, and shortness of breath on 3 occasions shortly after taking vardenafil 10 mg.

Reviewer's comment: This is the only patient who developed significant symptoms which could be attributed to an allergic reaction.

Patient 100250-017-009 had an SAE of coronary artery disorder and ST depression. This 64-year-old man with diabetes and hypertension developed intermittent chest discomfort starting 2 days after his last dose of study drug. An EKG several days later at the last scheduled visit revealed new ST depressions. He waqs subsequently diagnosed with CAD and underwent CABG. The investigator assessed the event as possibly related to study drug. This reviewer agrees.

Patient 100313-028-014 was a 60-year-old man with a history of type 2 diabetes and hypertension who developed symptoms of slurred speech, left hemiparesis, and headache while at work and was hospitalized for 2 days. He had been taking vardenafil 10 mg for 2 months. The last dose was taken on the day before the event. At the time of hospital admission, he was in hypertensive crisis with a BP of 226/108. During the study, his blood pressure had been normal. A CT scan showed no evidence of intracerebral hemorrhage. Relation of drug to the event was considered possible by the investigator and this reviewer agrees.

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 bypass surgery. He developed weakness of the left upper extremity 2 days after his last dose of 10 mg vardenafil. He waqs hospitalized and a CT scan showed evidence of a previous left lacunar thalamic infarct but no new infarct. An ultrasound of the carotid arteries showed bilateral plaque formation. The investigator believed there was no relationship of drug to the event, this reviewer believes a relationship is possible.

Patient 100249-044-057 was a 60-year-old man with a history of BPH, hypercholesterolemia, nephrolithiasis, and lumbar compression fracture who took 5 doses of study drug (vardenafil 5 mg) between June 1 and June 7, 2000. He was hospitalized on June 87, 2000, after an episode of syncope. He had taken his last dose of study drug at 11:00 PM on June 7, 2000. On June 7 he stopped taking terazosin and started finasteride. His blood pressure had been normal throughout the study. At the time of hospital admission, his BP was 92/50 mmHg. His hemoglobin and hematocrit values (11.5/33.9) on June 8 were lower than previous values (13/34). The syncopal event was considered as possibly related to study drug and the reviewer agrees.

Patient 10232-004-0030 was a 47-year-old man (history of cocaine abuse and depression) experienced increased LFT's beginning on the day of randomization and hyperglycemia beginning approximately 1 month after the beginning of study drug administration. At randomization, the ALT was 287 U/L. Ten days later the ALT was 109 U/L. For 2 days prior to randomization he had taken 2 g acetaminophen/day. Approximately 1 month after randomization, his ALT was 131 U/L and his glucose was 418 mg/dL. (He had polyuria prior to randomization.) He was discontinued from the study. ALT and AST at Visits 1, 2, 3, and 4 were 65 and 22, 287 and 114, 131 and 46, and 129 and 68. The investigator believed that the relationship to study drug was "possible."

Reviewer's comment: This patient s ALT and AST were elevated at randomization. This reviewer believes that the relationship to study drug is unlikely.

Amnesia was rported by patient 100250-043-005. After taking a 20 mg dose of vardenafil. The next day he noted impaired memory for events from the previous

day and was seen by a physician. The "symptoms were not apparent" to the physicain and the examination was negative. The patient discontinued the study.

Patient 100250-904-008 complained of numbness on the right side of his body 1 day after a dose of study medication. This 48-year-old man had a history of type 2 diabetes mellitus, spondylosis, osteoarthritis, depression, insomnia, asthma, diabetic retinopathy, pancreatitis, and gastroesophageal reflux. He took a dose of study drug (20 mg vardenafil) the day before the onset of the event, the day of onset, and subsequently took 4 more doses. He was evaluated by a neurologist. He was perscribed aspirin and study medication was discontinued. The investigator rated the event as possibly related to study drug and the reviewer agrees.

Patient 10125-38-002 experienced headache, dry mouth, and dyspepsia after nearly every intake of study drug (10 or 20 mg vardenafil – blinded). He subsequently developed "gastritis" after study drug ingestion and requested to be withdrawn from the study.

The incidence of serious adverse events by dose (Safety Pool 1 – placebo controlled trials which studied all 3 doses of vardenafil) is shown in Table 10.

Table 10.

Table 7-31 Pool 1: Incidence Rates by Dose of Serious Treatment Emergent Adverse Events by Dose (Events with at Least 2 Cases in One Treatment Group)

Adverse Event	Placebo n=342	Vardenafil 5 mg n=350	Vardenafil 10 mg n=358	Vardenafil 20 mg n=351	Total Vardenafil n=1059
Any Event	18 (5.3%)	10 (2.9%)	11 (3.1%)	13 (3.7%)	34 (3.2%)
Hernia	3 (0.9%)	0 (0.0%)	1 (0.3%)	2 (0.6%)	3 (0.3%)
Chest Pain	2 (0.6%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	1 (<.1%)
Syncope	1 (0.3%)	1 (0.3%)	1 (0.3%)	0 (0.0%)	2 (0.2%)
Cholelithiasis	0 (0.0%)	1 (0.3%)	1 (0.3%)	0 (0.0%)	2 (0.2%)
Diabetes Mellitus	3 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	1 (< 1%)
Hyperglycemia	0 (0.0%)	1 (0.3%)	1 (0.3%)	0 (0.0%)	2 (0.2%)

Pool 1, Table 2/1.11

These adverse events as well as other "clinically significant" adverse events are discussed in the individual study reviews (see Appendices A and B.)

Premature discontinuation:

The reasons for premature study termination are shown in Table 11.

Table 7-26 Pool 3: Reason for Premature Termination from Study

	Placebo (n=.793) n (%)	Vardenafil (n=1812) n (%)
Premature Termination	211 (26.6%)	325 (17.9%)
Reason for Premature Termination		
Adverse Event	11 (1.4%)	67 (3.7%)
Consent Withdrawn	54 (6.8%)	78 (4.3%)
Insufficient Therapeutic Effect	89 (11.2%)	79 (4.4%)
Lost to Follow Up	31 (3.9%)	54 (3.0%)
Other	26 (3.3%)	47 (2.6%)

Pool 3, Table 1/2.2

Reasons for premature discontinuation by dose of study drug are shown in Table 12.

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Table 12.

Table 7-27 Pool 1 Reason for Premature Termination from Study Displayed by Dose of Vardenafil

	Placebo n=342 n (%)	Vardenafil 5 mg n=350 n (%)	Vardenafil 10 mg n=358 n (%)	Vardenafil 20 mg n=351 n (%)	Total Vardenafil n=1059 n (%)
Premature Termination	111 (32.5)	76 (21.7)	59 (16.5)	76 (21.7)	211 (19.9)
Reason for Premature Termination					
Adverse Events	6 (1.8)	10 (2.9)	11 (3.1)	24 (6.8)	45 (4.2)
Consent Withdrawn	31 (9.1)	17 (4.9)	16 (4.5)	15 (4.3)	48 (4.5)
Insufficient Therapeutic Effect	46 (13.5)	26 (7.4)	12 (3.4)	13 (3.7)	51 (4.8)
Lost to Follow Up	20 (5.8)	11 (3.1)	17 (4.7)	11 (3.1)	39 (3.7)
Other	8 (2.3)	12 (3.4)	3 (0.8)	13 (3.7)	29 (2.6)

Pool 1, Table 1/2.2

The incidence rate by dose for treatmen emergent adverse events leading to discontinuation are shown in Table 13.

Table 13.

Table 7-29 Pool 1: 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)

Adverse Event	Placebo n=342	Vardenafil 5 mg n=350	Vardenafil 10 mg n=358	Vardenafil 20 mg n=351	Total Vardenafil n=1059
Any Event	7 (2.0%)	8 (2.3%)	9 (2.5%)	23 (6.6%)	40 (3.8%)
Headache	0 (0.0%)	3 (0.9%)	0 (0.0%)	4 (1.1%)	7 (0.7%)
Abdominal Pain	0 (0.0%)	0 (0.0%)	1 (0.3%)	1 (0.3%)	2 (0.2%)
Tachycardia	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.6%)	2 (0.2%)
Hypertension	0 (0.0%)	1 (0.3%)	0 (0.0%)	1 (0.3%)	2 (0.2%)
Vasodilatation	1 (0.3%)	0 (0.0%)	1 (0.3%)	1 (0.3%)	2 (0.2%)
Abnormal Liver Function Tests	1 (0.3%)	0 (0.0%)	3 (0.8%)	1 (0.3%)	4 (0.4%)
Nausea	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.9%)	3 (0.3%)
Dizziness	0 (0.0%)	1 (0.3%)	0 (0.0%)	1 (0.3%)	2 (0.2%)
Hypertonia	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.6%)	2 (0.2%)
Hypesthesia	0 (0.0%)	0 (0.0%)	2 (0.6%)	0 (0.0%)	2 (0.2%)
Rhinitis	0 (0.0%)	0 (0.0%)	1 (0.3%)	2 (0.6%)	3 (0.3%)
Sweating	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.6%)	2 (0.2%)
Kidney Calculus	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.6%)	2 (0.2%)

Pool 1, Table 2/1.9

1) Effect of vardenafil on the QT interval:

The sponsor retrospectively evaluated 8 Phase 1 and 2 studies in which EKG's had been performed and included manual (computer assisted) readings of the EKG's in the ISS (Appendix 18.1). This information included QT, QTc Bazett, and QTc Fridericia data. All of these trials were reviewed (see Appendix L).
A summary of these (manually read and data provided in ISS Appendix 18.1) studies is shown in Table 14.

Table 14. Vardenafil studies from which manually read ECG's were obtained.

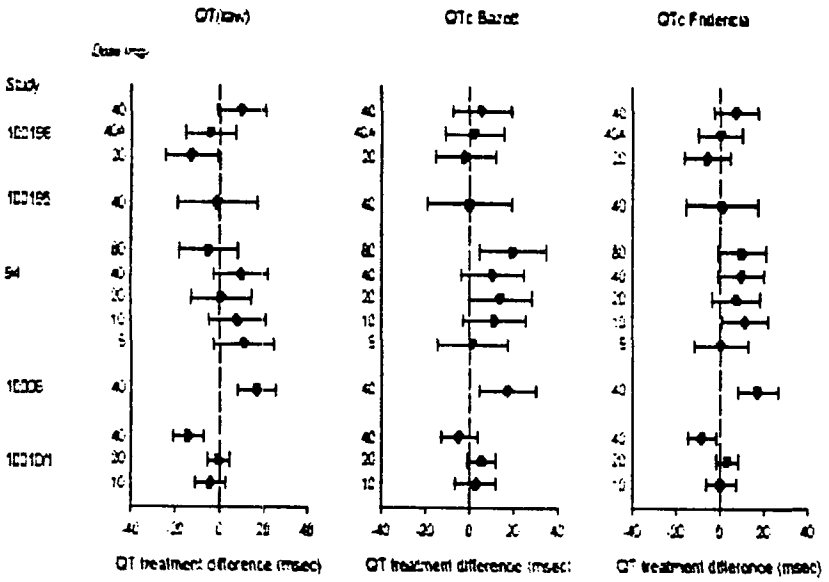
Study	Population	Timing (hours) in relation to dosing	Plac	5 mg	10 mg	20 mg	40 mg	80 mg
Single dose								
94	Healthy	Pre, 1	17	5	6	6	6	5
10006	Healthy	Pre, 1	8				16	
10104	Healthy	Pre, 1				12		-
10229	Healthy	Pre, 1				12		
10010/1	Patients	Pre, 2.5, 4, 6, 12, 24	44		21	43	23	
100195	Healthy	Pre, 0.5, 1, 2, 4	6[a]				18*	
100196	Healthy	Pre, 2, 4	12			12	26	
Totals			*87*	*5*	*27*	*85*	*89*	*5*
Multiple dose								
10006 Day 13	Healthy	Pre, 1	4				7	
196 Day 31	Healthy	Pre, 2, 4	11			11	25	

The increase in heart rate produced by vardenafil complicates the analysis of the QT data. In addition to providing an assessment of the effect of vardenafil on the rate corrected QTc, the QT-RR relationship for studies 10010 and 10011 was determined. A significant drawback to the study design of 10010 and 10011, however, is the fact that the first post-dosing ECG was obtained at 2.5 hours and the mean T_{max} of vardenafil is less than 1 hour.

Least squares mean QT data with 95 % confidence intervals (with Bazett corrected and Fridericia corrected QT interval data) are provided in Figure 1. No positive control group was incorporated into any of the study designs.

Figure 1.

Figure 4-1: LS mean QT data with 95% confidence intervals



Symbols are LS mean QTvar-QTpla
Error bars indicate 95% CI
40A indicates alternate day cohort in Study 100196

Summary of QT studies:

1) The increase in heart rate produced by vardenafil complicates the analysis of the QT interval changes.
2) The design of several of the studies is flawed with respect to analyzing the effect of vardenafil on the QT interval. Neither of the 2 trials involving CYP 3A4 inhibitors contained a placebo control group. Thus, the data from the ketoconazole trial (Trial # 10229) and the erythromycin trial (Trial

#101.04) are difficult to interpret. The C_{max} of vardenafil increases 4-fold when administered with ketoconazole. With regard to QTc Bazett, the mean change at one hour from the pre-dose value was 6.9 msec for vardenafil 20 mg and 18.2 msec for 5 mg vardenafil plus ketoconazole. The corresponding values for QTc Fridericia at one hour were 4.8 msec for vardenafil 20 mg and 12.8 msec for 5 mg vardenafil plus ketoconazole. The C_{max} of vardenafil increaes 3-fold when administered with erythromycin. With regard to QTc Bazett, the mean change at one hour from the pre-dose value was 14.9 msec for vardenafil 20 mg and 5.8 msec for 5 mg vardenafil plus erythromycin. The corresponding values for QTc Fridericia at one hour were 11.5 msec for vardenafil 20 mg and 3.9 msec for 5 mg vardenafil plus ketoconazole. In Trial 10229, the 18.2 (Bazett) and 12.8 (Fridericia) msec increases seen with 5 mg vardenafil and ketoconazole are concerning but difficult to evaluate with no placebo group. The same can be said for the 14.9 (Bazett) and 11.5 (Fridericia) msec increases seen in the 20 mg vardenafil group in Trial 10104.

3) Only 5 patients received an 80 mg dose and all of these patients were enrolled in Trial 94. Trial 94 was the only study which evaluated EKG changes at doses of vardenafil above 40 mg. Five patients were studied at 80 mg and 6 at 40 mg vardenafil (no patients were evaluated at doses between 40 and 80 mg). The QTc Bazett during the 80 mg dose was +14 msec over baseline at 1 hour compared to –3.0 msec for placebo. When corrected for heart rate by Fridericia's formula, the QTc changes from baseline were in the 5 to 12 msec range for the 10, 20, 40, and 80 mg doses and –0.8 msec for placebo. The QTc Fridericia changes do not appear to be dose dependent. This reviewer is unable to exclude an effect of vardenafil based on the results of Trial 94.
4) The largest amount of data was collected in Trials 10010 and 10011. The 20 mg vardenafil data shows a 1.3 msec mean increase over the pre-dose value for QTc Bazett at 2.5 hours and a 0.5 msec increase for placebo. The 40 mg data show a –2.9 msec difference from baseline at 2.5 hours. With respect to QTc Fridericia, at 2.5 hours the mean difference from pre-dose is –3.2 msec in the 40 mg group and +3.6 msec in the 20 mg group. The 2.5 hour placebo change is +2.9 compared to baseline. Although there appears to be no significant effect on the QT interval in Trials 10010 and 10011, the first EKG was performed at 2.5 hours post-dosing and the EKG's would, therefore, not be obtained at C_{max}.
5) With respect to QT data obtained following the 20 and 40 mg doses of vardenafil, the sponsor lists 85 total patients in the 20 mg groups and 89 total patients in the 40 mg groups. If patients from Trials 10104 (erytromycin trial) and 10229 (ketoconazole trial) are excluded because there was no placebo group and patients from Trials 10010 and 10011 are excluded because the first EKG was performed at 2.5 hours post-dosing, 18 patients remain in the 20 mg group and 66 patients remain in the 40 mg group.

Study	Relation to dosing	20 mg	40mg
94	Pre, 1 hour	6	6
10006	Pre, 1 hour	0	16
100195	Pre, 0.5, 1, 2, 4 hr.	0	18
100196	Pre, 2, 4 hours	12	26

In Trial 94, the 20 and 40 mg groups all had QTc Bazetts and QTc Fridericia corrected QT intervals in the + 6 to +14 range with placebo values of –3.0 and –0.8 msec for Bazett and Fridericia, respectively. Although no dose effect is seen, this reviewer can not rule out an effect of vardenafil in this trial.

In Trial 10006 which studied the 40 mg dose, both Bazett and Fridericia mean values are approximately +3 msec at the Day1, Hour1 reading. The placebo values for the same time frame are –15 and –14 msec. The large negative placebo results make interpretation of the data difficult.

In Trial 10195, the Bazett and Fridericia mean values are 3 and 1 msec greater than placebo at 30 minutes and 3 and –1 msec different from placebo at 1 hour.

In Trial 10196, at 2 hours (the time of the first EKG) the mean Bazett values are –1.3 for placebo, 1.3 for 20 mg and 7.2 for 40 mg. The Fridericia mean values are 0.4 for placebo, -2.1 for 20 mg, and +9.4 for 40 mg.

6) This reviewer is unable to exclude an effect of 40mg vardenafil on the QT interval in Trials 94 and 10196.

In summary, following review of the data provided (see Appendix L), this reviewer is unable to exclude an effect of vardenafil on the QT interval. A consultation was obtained from the CardioRenal Division. The consultant concluded that "although the available data raise no concern regarding arrhythmogenic potential, the data are not particularly compelling that such a risk has been ruled out."

2) Vardenafil nitrate interaction:

Although nitrates are a contraindication to vardenafil use, some men with cardiovascular disease using vardenafil will experience emergency situations where use of nitrates is indicated. Information is needed to label the effects of nitrates on blood pressure in patients taking vardenafil. The effect of 0.4 mg nitroglycerin on vital signs was determined in 18 healthy men (mean age 48 years; range 40 to 65 years) at 24, 8, 4, and 1 hour after dosing with study drug (vardenafil 10 mg or placebo). This trial (#100304) is reviewed in Appendix I. The effect of nitroglycerin on systolic and diastolic blood pressure in patients taking 10 mg vardenafil was not clinically significant (1 to 2 mm range) at any of the time frames evaluated (1, 4, 8, and 24 hours). The sponsor did not submit data for 20 mg vardenafil.

3) Alcohol interaction:

Trial 10348, an alcohol interaction study, is reviewed in Appendix K. A 20 mg dose of vardenafil was given with an alcohol dose of 0.5g/kg. This dose of alcohol produced blood alcohol levels which were just below the legal limit for intoxication. No clinically significant changes in vital signs were observed.

4) Myalgias and back pain:

Back pain and myalgia are observed with vardenafil, primarily with high and frequent dosing (for example, 40 mg bid). During Part 2 of Trial 10006 (patients dosed with 40 mg vardenafil bid), all eight patients taking vardenafil suffered from myalgia and/or back pain from treatment day 2 or 3 onwards. None of the placebo patients (N=4) experienced back pain. Because all of the drug treated patients and none of the placebo treated patients developed significant back pain, this portion of the study was terminated on Day 4. On the same day the study was discontinued, a consultant neurologist diagnosed an "isolated myalgia of the long muscles of the back and in the legs without any muscle weakness or neurological deficits." In this same trial (10006), 5 of 7 patients in the 40 mg/day dose (given for 14 days) group experienced back pain.

In clinical pharmacology Trial 100196, back pain was reported in 0/12 placebo patients, 3/12 20 mg/day patients, 3/13 40 mg every other day patients, and 7/13 40 mg vardenafil/day patients. In the 20 mg group, in 2 of the 3 patients the back pain was rated as "mild" and in the third patient the back pain was rated as "moderate."

In the Phase 3 clinical trials, back pain was not observed more commonly with vardenafil at doses up to 20 mg than with placebo. The incidence of myalgia/back pain at doses of 5 to 20 mg (Safety Pool 3 – all placebo controlled studies) was placebo 2.4% and vardenafil 2.2% for back pain and placebo 0.3% and vardenafil 0.7% for myalgia.

In the 2 Phase 3 placebo-controlled studies which evaluated the 5, 10, and 20 mg doses of vardenafil, the incidence of back pain is shown in Table 15:

Table 15. Incidence and severity of back pain in Trials 100249 and 10128.

Trial	Placebo	Vard. 5 mg	Vard. 10 mg	Vard. 20 mg
10249	6 (3%) (2 mild, 3 moderate, 1 severe)	6 (3%) (3 mild, 3 moderate)	9 (5%) (8 mild, 1 moderate)	5 (3%) (2 mild, 3 moderate)
10128	5 (3%) (3 mild, 2 moderate)	5 (3%) (2 mild, 1 moderate, 2 severe)	2 (1%) (2 mild)	1 (<1%) (1 severe)

The etiology of back pain seen with vardenafil exposure is unknown. The back pain subsides within 48 hours of discontinuing the drug. There is no associated significant

CK increase. In the Phase 3 clinical trials, the incidence of back pain was not different from placebo. In the opinion of this reviewer, the etiology of back pain seen with vardenafil should be further evaluated (by Phase 4 commitment) but is not an approvability issue.

5) Ophthalmology adverse events:

Visual adverse events are known to occur with PDE5 inhibitors. A consultation regarding ophthalmologic safety was requested from ophthalmology. The recommendations of the consultant were: 1) "From an ophthalmologic perspective, there is no objection to the approval of this NDA provided that the labeling is consistent with other phosphodiesterase inhibitors" and 2) "It is recommended that repeated dose studies evaluating the effect of vardenafil on retinal function be conducted and submitted for review."

6) Effect of vardenafil on the response to exercise in patients with coronary artery disease:

Trials 100408 (vardenafil 20 mg) and 100302 (vardenafil 10 mg) evaluated the effect of vardenafil on the cardiovascular response to exercise in patients with coronary artery disease. These studies are reviewed in Appendix K. These trials did not demonstrate any adverse effect of vardenafil 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.

7) Effect of vardenafil on liver function tests:

One patient in Clinical Pharmacology Trial 10006 experienced an elevation in liver function tests which was considered by the investigator to not be related to study drug. This patient (#10) had normal ALT and AST values at baseline. On treatment day 7 the enzymes were slightly elevated. After a further increase on Day 8 (AST 24 U/L; normal value <19 and ALT 45.8 U/L; normal value <23) drug was discontinued. Three days after the drug was stopped, ALT was 114.6 and AST was 54.9. He was hospitalized for 24 hours for "further control and diagnostics." Maximum AST was 66 U/L on Day 12 and ALT was 142 U/L also on Day 12. On follow-up, all values returned to the normal range. Ultrasound of the liver was normal. No etiology for the increased transaminases was determined. Although the sponsor considers that it is "very unlikely" that this adverse event was related to study drug, this reviewer believes that a relationship to vardenafil can not be excluded.

The incidence of high AST, ALT, and CK values which occurred in Safety Pool 3 (all placebo-controlled studies using vardenafil 5, 10, or 20 mg (Trials 100249, 10128, 100250, 100285, and 10232) is shown in Table 16.

Table 16. Incidence of elevated AST, ALT, and CK values in Pool 3.

Laboratory study	Placebo N=793 (%)	Vardenafil 1812 (%)
Creatine kinase (CK,CPK)	122/598 (20.4%)	313/1402 (22.3%)
SGOT/AST	57/698 (8.20%)	139/1630 (8.5%)
SGPT/ALT	66/664 (9.9%)	159/1565 (10.2%)

"Potentially clinically significant chemistry laboratory abnormalities" for patients in Safety Pool 3 are shown in Table 17.

Table 17. Potentially Clinically Significant Chemistry Laboratory Abnormalities in Safety Pool 3.

Table 8-10 Pool 3: Incidence Rates of Treatment-Emergent Potentially Clinically Significant Chemistry Laboratory Abnormalities

	Lab Variable	Placebo	Vardenafil
CK	>3xULN	16/748 (2.1%)	50/1745 (2.9%)
	>5xULN	8/752 (1.1%)	18/1762 (1.0%)
	>10xULN	2/753 (0.3%)	5/1764 (0.3%)
SGOT/AST	>3xULN	2/753 (0.3%)	4/1760 (0.2%)
	>5xULN	1/753 (0.1%)	3/1764 (0.2%)
	>10xULN	0/754 (0%)	2/1765 (0.1%)
SGPT/ALT	>3xULN	8/752 (1.1%)	4/1760 (0.2%)
	>5xULN	2/753 (0.3%)	2/1764 (0.1%)
	>10xULN	0/754 (0%)	0/1765 (0%)

Pool 3. Table 3/3

Two patients experienced serious adverse events of abnormal liver function tests. Both patients had a history of alcohol consumption relating temporally to the abnormal liver function tests. (See Appendix N).

This reviewer believes that the incidence of clinically significant elevations in liver function tests is low and, in the vast majority of patients, additional factors which could have contributed to the increases are present. There does not appear to be a relationship of dose of vardenafil administered and clinically significant elevations of LFT's. In the opinion of this reviewer, increased transaminases may occur at a low incidence in the broad population and information concerning transaminases should be included in the label.

8) Effect of vardenafil on CK increase

The incidence of CK elevation in Safety Pool 3 and the incidence "potentially clinically significant CK elevations are shown in Tables 5 and 6 above.

One patient experienced an elevation of CK to 18690 U/L and another patient had an elevation to 29940 U/L during the clinical trials. Both patients had recently participated in recent strenous physical exertion and are discussed in Appendix N.

Frequent adverse events:

The most frequent adverse events were those which are known to be associated with PDE5 inhibitors. The incidence of these adverse effects (in the 2 pivotal trials which evaluated the 5, 10, and 20 mg doses of vardenafil) is shown in Table 18.

Table 18. Incidence rates (%) by dose of drug-related treatment emergent adverse events (judged by the investigator as "possibly" or "probably" related to study drug") 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

Reviewer's comment: These frequent adverse events demonstrate a relationship to vardenafil dose.

7.4 Postmarketing Surveillance

Not applicable.

7.5 Safety Update

No new safety concerns were raised with the safety update. The following safety report was submitted during the review process:

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."

7.6 Labeling Safety Issues

Labeling changes regarding use in the elderly, in patients with hepatic impairment, and when the drug is used with CYP 3A4 inhibitors have been discussed above.

8.0 Dosing and Regimen Issues

In addition to the 4 major efficacy trials, two major dose–ranging studies are submitted to support the proposed doses of vardenafil (5, 10, and 20 mg). Trial 100199 was a Phase 2b study which enrolled healthier patients (no significant cardiovascular co-morbidities) than were enrolled in the subsequent Phase 3 trials. Vardenafil doses evaluated were 5, 10, and 20 mg. Primary endpoints were questions 3 and 4 of the IIEF. The treatment differences between vardenafil 5 mg and 10 mg and between vardenafil 10 and 20 mg were not statistically significant. The 20 mg vardenafil dose showed a trend toward improvement over the 5 mg dose for penetration ($p=0.087$) and maintenance of erection ($p=0.082$). Since Trial 100199 showed that vardenafil 5 mg was significantly more effective than placebo and not significantly less effective than vardenafil 10 mg, another study (Trial 10232) was performed to explore the lower end of the vardenafil dose range (2.5 and 5 mg). This study used the same patient population and the same primary efficacy measures as the major Phase 3 efficacy trials. "Because the 2.5 mg vardenafil dose showed relatively small treatment differences of questionable clinical value over placebo and because it conveyed no obvious safety advantage over the 5 mg dose, the development of the 2.5 mg dose was not pursued further."

With respect to the high end of the proposed doses, in 3 of the 4 major trials, the dose of 20 mg is not clinically or statistically superior to 10 mg. In Trial 100250 (diabetic patients with erectile dysfunction), the difference between 20 and 10 mg for the EF domain of the IIEF was statistically different in favor of the 20 mg dose. The data for SEP 2 and SEP 3 were marginally numerically superior for the 20 mg dose in this trial, but the differences did not reach statistical significance. None of the "pivotal" studies was designed to specifically compare the 10 and 20 mg doses of vardenafil.

Reviewer's comment: The reviewer believes that the proposed doses are acceptable.

9.0 Use in Special Populations

9.1 Effects of Gender, Age, and Race:

Gender: Vardenafil is indicated only for the treatment of men with erectile dysfunction.

Age: There was >50% increase in AUC and >30% increase in C_{max} in patients greater than 65 years of age. The clinical pharmacology reviewer recommends that a dose recommendation should be added to the label that "men over 65 years of age should not receive doses higher than 10 mg of vardenafil." Safety data from the clinical studies do not show any increased incidence of adverse events in men >65 years of age compared to those < 65 years of age. Because the safety data do not indicate any significant concern for the 20 mg dose in patients >65 years of age, this reviewer does not believe that any dose adjustment is required in these patients.

Race/ethnicity: The vast majority of patients in both the vardenafil and placebo treatment groups were Caucasian. The number of patients in racial sub-groups other than Caucasians was too small to detect any meaningful differences in the rates of adverse events in vardenafil treated patients across racial subgroups.

9.2 Pediatric Program: Vardenafil is indicated only for men with erectile dysfunction. The sponsor has requested a pediatric waiver.

9.3 Data Available or Needed in Other Populations Such as Renal or Hepatic Compromised Patients or use in Pregnancy:

Effect of impaired renal function: Renal impairment does not have a significant effect on vardenafil exposure, and the clinical pharmacology reviewer believes that dose adjustment is not required in renal impairment. This reviewer agrees. Vardenafil has not been studied in patients on dialysis.

Effect of hepatic impairment: Based on the results showing increase in drug exposure (approximately 2 ½ times the AUC and C_{max}), the clinical pharmacology reviewer believes that the starting dose of vardenafil in the moderately hepatic impaired patient should be 5 mg, and such patients should not be given doses higher than 10 mg. This reviewer agrees with the clinical pharmacology reviewer in recommending that moderately hepatic-impaired patients not be given doses higher than 10 mg (not 20 mg as recommended in the proposed label). (Exposure in patients with moderate hepatic impairment given a 20 mg dose would be equivalent to a 50 mg dose in patients without hepatic impairment. Limited safety data are available for this dose level.) Patients with severe hepatic impairment have not been evaluated.

Pregnancy: Vardenafil is not indicated for use in women.

10.1 Conclusions Regarding Safety and Efficacy

Vardenafil in doses of 5, 10, and 20 mg was shown in 4 adequate, well-controlled studies to be effective in the treatment of erectile dysfunction. This reviewer is unable to exclude an effect of vardenafil on the QT interval. Drug exposure is anticipated to be high in patients taking concomitant CYP 3A4 inhibitors. The consultant from the CardioRenal Division concluded that "although the available data raise no concern regarding arrhythmogenic potential, the data are not particularly compelling that such a risk has been ruled out." No nitrate interaction data is available for the 20 mg dose of vardenafil.

10.2 Recommendations on Approvability:

In the opinion of this reviewer, from a clinical perspective, vardenafil in doses of 5, 10, and 20 mg should receive an approvable action for the indication "treatment of erectile dysfunction." The major reason for this decision is the fact that this reviewer is unable to exclude an effect on the QT interval and high drug exposure is seen in patients taking CYP 3A4 inhibitors. In addition, for the 20 mg dose, the nitrate interaction study evaluated 10, but not 20 mg, of vardenafil.

The sponsor can correct these deficiencies by:

1) Performing an adequately designed, placebo-controlled study to evaluate the effect of vardenafil on the QT interval using doses of at least 80 mg.
2) Performing a nitrate interaction study utilizing a dose of 20 mg vardenafil.

In addition, the sponsor should attempt to elucidate the etiology of back pain associated with vardenafil. In the opinion of this reviewer, this is not an approvability issue.

Finally, additional Phase 4 studies should be conducted to evaluate the potential effect on visual function of repeated drug administration.

Labeling: Labeling cannot be finalized because there is inadequate information to support marketing approval for this product.

APPEARS THIS WAY
ON ORIGINAL

Appendix A – Clinical Trial 100249 ("A randomized, double-blind, placebo-controlled, multicenter, fixed-dose, parallel group, 6 month comparison study to investigate the efficacy and safety of the phosphodiesterase type V inhibitor BAY 38-9456 in males with erectile dysfunction") (Trial start: 3/29/2000; trial completion 3/2/2001)

A.1 Objectives: 1) to assess the efficacy and safety of the phosphodiesterase type V (PDE5) inhibitor vardenafil in the treatment of men with erectile dysfunction (ED) and 2) to determine plasma levels of vardenafil after dosing in order to perform population pharmacokinetic analysis on the total population of subjects studied in the clinical development program.

A.2 Design and conduct summary: This study was a multicenter (54 United States and Canadian sites), randomized, double-blind, placebo-controlled, fixed-dose, 4-arm, parallel-group, 6-month comparison of vardenafil 5 mg, 10 mg, and 20 mg and placebo in men with ED for more than 6 months. ED was defined as the inability to achieve or maintain penile erection sufficient for satisfactory sexual performance. The study consisted of 3 phases: 1) baseline: 4 weeks without treatment 2) treatment phase: 26 weeks of double-blind treatment (vardenafil 5 mg, 10 mg, or 20 mg or placebo) and 3) follow-up phase: 7 days from the date of the last dose in which to collect data concerning serious adverse events.

Of the 1311 patients screened, 506 discontinued or were dropped during the 4-week baseline phase and 805 were randomized (197 to placebo, 205 to vardenafil 5 mg, 206 to vardenafil 10 mg, and 197 to vardenafil 20 mg). Patients were instructed to take drug about 1 hour prior to intended sexual intercourse, with not more than one dose to be taken within a calendar day. There were 3 primary efficacy endpoints: 1) erectile function domain score of the IIEF at week 12 using LOCF 2) success in penetration at Week 12 (from patient diary) and 3) success in maintaining erection at Week 12 (from patient diary).

Patients were seen at Week –4(screening), 0 (randomization), and 4, 8, 12, 8, and 26. IIEF and diary data were collected at each visit beginning at Week 0. Vital signs were determined at each visit. Hematology and chemistry values were determined at each visit except Week 8. A 12-lead EKG was performed at screening and at weeks 0, 4, 12, 18, and 26. Fasting serum cholesterol and fasting serum triglycerides were analyzed at screening and at Week 26. One blood sample was obtained at baseline (Week 0) and 2 more at each of 2 subsequent visits (Weeks 4 and 12) for determination of population PK. The first blood sample was collected between 15 and 45 minutes and the second between 60 and 180 minutes post-dosing.

A.3 Study population: The study population was men aged 18 years or greater with at least a 6 month history of erectile dysfunction. The baseline characteristics of the study population are shown in Table 1.

Table 1. Baseline characteristics of randomized patients.

	Placebo (N=182)	Vardenafil 5 mg (N=193)	Vardenafil 10 mg (N=199)	Vardenafil 20 mg (N=188)
Race % Caucasian	77%	77%	80%	82%
Age (years)	57	57	57	58
EF domain of IIEF	13.7	12.6	13.4	12.8
"Insert penis into partners vagina?" (mean of per-patient % "yes")	46.3	42.6	45.6	41.2
"Erection long enough for successful intercourse?" (mean of per-patient % "yes")	15.7	15.0	14.6	15.2

Approximately 79% of the study population was Caucasian, 13% Black, and 4% Hispanic. Approximately 70% of patients had previously used sildenafil, which had improved erections in 100% of these patients.

Reviewer's comment: The fact that 70% of patients had previously used sildenafil and that all of them had responded to this medication may have skewed the study population.

A.4 Inclusion and exclusion criteria: Inclusion criteria included: 1) men 18 years of age or older with ED and 2) at least 4 attempts at sexual intercourse on 4 separate days during the untreated baseline period. At least 50% of these attempts had to have been unsuccessful, that is, failed penetration or maintenance of an erection. Exclusion criteria included: 1) primary hypoactive sexual desire 2) ED after spinal cord injury 3) history of radical prostatectomy 4) retinitis pigmentosa 5) history of positive test for hepatitis B or C 6) unstable angina pectoris 7) history of myocardial infarction, stroke, electrocardiographic ischemia, or life-threatening arrhythmia within the prior 6 months 8) uncontrolled atrial tachyarrhythmia at screening (ventricular response >100 beats per minute) 9) severe chronic liver disease or liver function abnormalities (AST or ALT > 3 x ULN) 10) clinically significant chronic hematologic disease or bleeding disorder 11) significant peptic ulcer disease within 1 year 12) resting hypotension (SBP < 90 mmHg) or hypertension (resting SBP > 170 mmHg or a resting DBP > 110 mmHg) 13)

symptomatic postural hypotension within 6 months of screening 14) poorly controlled diabetes mellitus (HbA_{1C} > 12%) 15) inadequately treated hyperthyroidism or hypothyroidism 16) history of non-skin cancer within the past 5 years 17) concomitant medications consisting of nitrates or nitric oxide donors, antiandrogens, anticoagulants (except antiplatelet drugs), androgens, Trazodone, sildenafil within 7 days of Visit 1, vardenafil before Visit 1 18) serum testosterone below lower limit of normal 19) serum creatinine >2.5 mg/dL 20) history of severe migraine headaches within the past 6 months and 21) history of unresponsiveness to sildenafil.

A.5 Primary and secondary endpoints: Primary efficacy endpoints were: 1) EF domain of the IIEF calculated as the sum of scores from questions 1-5 and 15 at Week 12 2) Success in penetration ("Were you able to insert your penis into the partner's vagina?" by patient diary from the start of study drug to Week 12 using overall per-patient success rate and 3) success in maintaining erection during intercourse ("Did your erection last long enough for you to have successful intercourse?" by patient diary from the start of study drug to Week 12, using the overall per-patient success rate. Secondary efficacy endpoints were: 1) EF domain scores of the IIEF at Week 12, as observed 2) EF domain scores of the IIEF at Weeks 4, 8, 18, and 26, as observed and LOCF 3) success in penetration and maintenance of erection by patient's diary from randomization to Week 12, as observed 4) success in penetration and maintenance of erection by patient's diary from randomization to Weeks 4, 8, 18, and 26, as observed and LOCF 5) success in penetration and maintenance of erection by patient's diary between Weeks 8 and 12, as observed and LOCF 6) other IIEF domain scores at Weeks 12 and 26, as observed and LOCF 7) scores for questions 3 and 4 of the IIEF at Weeks 4, 8, 12, 18, and 26, as observed and LOCF 8) scores for other questions on the IIEF at Weeks 12 and 26, as observed and LOCF 9) responses on the patient's diary concerning hardness of erections, overall satisfaction with sexual experience, and ejaculation at Weeks 12 and 26, as observed and LOCF 10) global assessment question at Weeks 12 and 26, as observed and LOCF 11) Fugl-Meyer quality of life questionnaire at Weeks 12 and 26, as observed and LOCF and 12) Center for Epidemiologic Studies Depression Scale at Weeks 12 and 26, as observed and LOCF.

A.6 Withdrawals, compliance, and protocol violations: In all, 1311 patients entered the screening phase, 506 patients discontinued from the screening phase of the study, and 805 patients were randomized. Five-hundred eight (63%) completed the study. The major reasons for discontinuation were "lost to follow-up," "insufficient therapeutic effect," and "consent withdrawn." Thirty-four patients (4%) discontinued because of an adverse event. More patients treated with vardenafil 20 mg compared with the other groups discontinued because of an adverse event and more patients in the placebo group discontinued because of withdrawn consent, insufficient therapeutic response, and loss to follow-up. The vast majority of protocol violations involved taking more than one dose of study medication per

calendar day. Eleven patients (1 in the placebo group, 4 in the vardenafil 5 mg group, 4 in the vardenafil 10 mg group, and 2 in the vardenafil 20 mg group) each took 3 or more doses in a calendar day. Specifically, one patient in the placebo group took 5 doses in 1 day on 3 different occasions; 4 patients in the vardenafil 5 mg group took 3 doses in 1 day (one patient on 2 different occasions and another patient on 4 different occasions); 3 patients in the vardenafil 10 mg group took 3 doses in 1 day (one patient on 2 different occasions) and another patient in this group took 3 doses in 1 day on 3 different occasions and 4 doses on 2 other occasions; and 2 patients in the vardenafil 20 mg goup took 3 doses in 1 day. The remainder of the patients took at most 2 doses in 1 calendar day. In all, multiple doses were taken on 467 patient-days.

A.7 Efficacy analysis:

The results of the efficacy analyses for the 3 primary endpoints are shown in Table 2.

Table 2. Results for primary efficacy parameters: IIEF EF domain at LOCF and overall per-patient diary results for penetration and maintenance questions at week 12 (ITT population).

	Placebo	Vardenafil 5 mg	Vardenafil 10 mg	Vardenafil 20 mg
EF domain of IIEF at week 12				
LS mean baseline	13.6	12.5	13.4	12.8
LS mean value	15.0	18.4*	20.6*	21.4*
Success in penetration at Week 12				
LS mean baseline	46.0	42.8	45.4	40.9
LS mean value	51.7	65.5*	75.5*	80.5*
Success in maintenance at Week 12				
LS mean baseline	14.9	14.0	14.6	14.7
LS mean value	32.2	50.6*	64.5*	64.5*

LS = least square
* = $p<0.0001$

Efficacy for the 3 primary endpoints was maintained through week 26. The differences between the means of each vardenafil group versus placebo at

weeks 12, 18, and 26 were smaller than the corresponding differences at Weeks 4 and 8.

Reviewer's comment: This reviewer agrees with the sponsor's assessment of smaller differences between drug groups and placebo at longer time intervals as being due to the fact that the dropout rate was much higher in the placebo than in the drug groups.

Secondary endpoints:

The Global Assessment Question "Has the treatment you have taking over the last 4 weeks improved your erection?" was answered "yes" in a greater percent of all drug dose group patients than by placebo patients ($p<0.0001$).

Dose response: In terms of the IIEF at Week 12, vardenafil 20 mg was statistically significantly better than the vardenafil 5 mg group for all of the IIEF questions and domain scores except for question 6 (frequency of attempts) and questions 11 and 12 (sexual desire and sexual desire domain score). Vardenafil 10 mg was statistically significantly better than vardenafil 5 mg for these same variables. Vardenafil 20 mg was not statistically significantly better than vardenafil 10 mg for any of the IIEF questions or domains. Vardenafil 20 mg was numerically better than vardenafil 10 mg for about half of the IIEF variables.

In terms of the Week 12 overall per-patient success rate for the diary questions in the ITT population, vardenafil 10 and 20 mg were statistically significantly better than vardenafil 5 mg for each question. Vardenafil 20 mg was numerically better than vardenafil 10 mg for each question, but no difference reached statistical significance.

A.8 Safety analysis:

A.8.1 Extent of exposure: The safety analysis includes 182 patients in the placebo group,193 in the vardenafil 5 mg group, 199 in the vardenafil 10 mg group, and 188 in the vardenafil 20 mg group. The mean duration of treatment in the placebo group was 109 days. This mean duration was shorter than in the vardenafil groups which ranged from 139 to 151 days. The mean total number of doses taken by patients in the placebo group was 30.7, compared with 50.8 to 53.1 doses in the vardenafil groups. The mean number of doses per patient-week was 2.2 to 2.3 doses per patient-week in the vardenafil groups.

A.8.2 Serious adverse events:

Deaths: There were no deaths during the trial.

Serious adverse events: Serious adverse events occurred in 10 (5%) placebo patients and 9 (5%), 6 (3%), and 8 (4%) of the 5, 10, and 20 mg vardenafil groups, respectively (Table 12.5 in study report narrative). In data listing Table 14.3.2/4, SAE's are listed for 13 placebo patients and for 13, 7, and 11 patients in the 5, 10, and 20 mg vardenafil groups. A listing of the SAE's is provided in Table 3.

Table 3. SAE's in 4 study groups

Placebo	Vardenafil 5 mg	Vardenafil 10 mg	Vardenafil 20 mg
1) GI hemorrhage	1) Arthritis	1) Cholecystitis	1) Kidney stone
2) Myocardial infarct	2) Prostate disorder	2) Elevated LFT's	2) Neoplasm
3) Hernia	3) Cholecystitis	3) Gastroenteritis	3) CNS neoplasm
4) Allergic reaction	4) Pneumonia	4) Atrial fib.	4) Pneumonia
5) Atrial fib.	5) Osteomyelitis	5) Aortic stenosis	5) Hernia
6) Arthritis	6) Vascular anomaly	6) Hernia	6) Myocardial infarct
7) Angina	7) Syncope	7) Syncope	7) Coronary occlusion
8) Hernia	8) Bone disorder		8) Congestive heart failure
9) Syncope	9) Abdominal pain		9) Prostate cancer
10) Musculoskeletal surgery	10) Chronic lymphocytic leukemia		10) Joint disorder
11) GI hemorrhage			11) Depression
12) Musculoskeletal surgery			
13) Cancer			

In the Vardenafil 5 mg group:

Syncope – Patient #44057 – This 60-year-old man (history of BPH and hypercholesterolemia) took 5 doses of study drug between June 1 and June 7, 2000. On June 8, 2000, he was hospitalized due to an episode of syncope. He had taken a dose of study medication at 11:00 PM on June 7, 2000. On June 7, 2000, he had stopped taking terazosin 10 mg and started taking finasteride 5 mg. Study drug was discontinued. Baseline hemoglobin was 13.0 g/dL. During his hospitalization for syncope, his hemoglobin was 11.5 and his hemoglobin was 13.2 at follow-up 20 days later. His BP was 92/50 mmHg during hospitalization (130/88 at previous study visit). Twenty days later his BP was 106/70. Results of a cardiac stress test were negative. Concomitant medications included Lescol (fluvastatin). The investigator rated the relationship to study drug as "possible."

Reviewer's comment: The reviewer agrees that relationship to study drug is possible.

In the vardenafil 10 mg group:

Increased liver function tests – Patient 4003 – This 47-year-old man (history of cocaine abuse and depression) experienced increased LFT's beginning on the day of randomization and hyperglycemia beginning approximately 1 month after the beginning of study drug administration. At randomization, the ALT was 287 U/L. Ten days later the ALT was 109 U/L. For 2 days prior to randomization he had taken 2 g acetaminophen/day. Approximately 1 month after randomization, his ALT was 131 U/L and his glucose was 418 mg/dL. (He had polyuria prior to randomization.) He was discontinued from the study. ALT and AST at Visits 1, 2, 3, and 4 were 65 and 22, 287 and 114, 131 and 46, and 129 and 68. The investigator believed that the relationship to study drug was "possible."

Reviewer's comment: This patients ALT and AST were elevated at randomization. This reviewer believes that the relationship to study drug is unlikely.

Syncope – Patient 27008 – This 67-year-old man (history of diabetes, hypertension, coronary artery disease, hypercholesterolemia, cardiac bypass, thrombocytopenia, and low WBC) had several syncopal episodes before being admitted to the hospital. The last dose of study drug was 1 day prior to the syncopal episodes. He underwent cardiac catheterization which revealed complete occlusion of the right and left anterior descending arteries and 95% proximal stenosis of the ramus artery and circumflex vessel. Significant left ventricular dysfunction was also diagnosed. He was taking 9 medications (primarily for diabetes and cardiovascular disease. The investigator rated the relationship of the syncopal episodes as "unlikely" related to study drug.

Reviewer's comment: The reviewer believes that a relationship to study drug is "possible."

Vardenafil 20 mg group:

Myocardial infarction – Patient # 29002 – This 62-year-old man experienced a myocardial infarction and was hospitalized on October 6, 2000. The last known dose of study medication was on September 5, 2000. The patient was dispensed study medication on September 6, 2000, but never returned the diary or unused medication and the last dose of study medication prior to the infarct was unknown. The patient was contacted and stated that he had had a bicycle accident 3 weeks prior to the diagnosis of the MI and both he and 3 physicians he had seen believed the chest pain was musculoskeletal. The patient never returned to the clinic. The investigator believed the relationship to study drug was "unlikely."

Reviewer's comment: The reviewer does not believe there is enough information to comment on the relationship of study drug to the event.

Coronary occlusion – Patient #29015 – This 61-year-old man (history of diabetes, cardiomegaly, "leaking" heart valves, and arthritis) was admitted to the hospital with unstable angina. Cardiac catheterization revealed significant coronary artery disease and he underwent bypass surgery. The last dose of study drug was taken 4 days prior to the event. The investigator rated the event as "unlikely" to be related to study drug.

Reviewer's comment: The reviewer agrees that the relationship of study drug to this event is "unlikely."

A.8.3. Discontinuations due to adverse events:

The discontinuation rates due to adverse events for the 4 groups of patients are shown in Table 4.

Table 4. Discontinuations due to adverse events

	Placebo (N=182)	Vardenafil 5 mg (N=193)	Vardenafil 10 mg (N=199)	Vardenafil 20 mg (N=188)
Discontinuation due to adverse event	4 (2%)	7 (4%)	7 (4%)	14 (7%)

No single adverse event led to discontinuation of study drug in more than 1 patient per treatment group, except for headache (2 patients each in the vardenafil 5 and 20 mg groups), abnormal liver function tests (3 patients for vardenafil 10 mg), nausea (2 patients for vardenafil 20 mg), hyperesthesia (2 patients for vardenafil 10 mg), and kidney stone (2 patients for vardenafil 20 mg).

A.8.4 Frequent adverse events: Headache, vasodilation, dyspepsia, and rhinitis were more frequent in the vardenafil groups than in the placebo group: each one of these events had an incidence at least 5% higher in one of the vardenafil groups compared with placebo. The rates of these 4 events increased with increasing vardenafil dose except for headache. Adverse events judged "possibly or probably" related to study drug by the investigator are shown in Table 5.

Table 5. Incidence of adverse events judged possibly or probably related to study drug by the investigator.

	Placebo (N=182)	Vardenafil 5 mg (N=193)	Vardenafil 10 mg (N=199)	Vardenafil 20 mg (N=188)
Headache	2 (1%)	13 (7%)	34 (17%)	33 (18%)
Vasodilation	0 (0%)	8 (4%)	19 (10%)	23 (12%)
Dyspepsia	0 (0%)	2 (1%)	5 (3%)	10 (5%)
Rhinitis	2 (1%)	3 (2%)	16 (8%)	17 (9%)

Myalgia occurred in 1 placebo patient, 1 vardenafil 5 mg patient, 4 vardenafil 10 mg patients, and 1 vardenafil 20 mg patient.
Abnormal vision occurred in no placebo patients, 1 vardenafil 5 mg patient, no vardenafil 10 mg patients, and 4 vardenafil 20 mg patients.

A.8.5 Clinically significant events:

The sponsor selected certain cardiovascular and visual events as "clinically significant." These events occurred in 9 (5%) placebo, 6 (3%) vardenafil 5 mg, 8 (4%) vardenafil 10 mg, and 19 (10%) vardenafil 20 mg. In the 20 mg vardenafil group, the 18 clinically significant events consisted of inverted T waves (1), tachycardia (1), lacrimation disorder (1), abnormal or blurred vision (5), refraction disorder (1), conjunctivitis (3), photophobia (1), chest pain (1), arrhythmia (2), atrial flutter (1), tachycardia (1), and hypotension (1).

Selected narratives from these events occurring at the 20 mg vardenafil dose are as follows:

Patient 010-006: This 67-year-old man with a history of HTN, CAD, gastroesophageal reflux, BPH, MI, hypothyroidism, hypercholesterolemia, CABG and a hydrocele was discontinued from the study after approximately 3 1/2 months on study drug due to inverted T-waves finding on the Visit 5 ECG. Earlier in the study, the patient had adverse events of intermittent chest pain and left bundle branch block. Stress test was negative for ischemia, and cardiac catheterization showed all 5 bypass grafts to be open. The cardiologist felt that the inverted T-waves were related to the patient's underlying cardiac rhythm and did not require further work-up; the investigator, however, decided to discontinue the patient from the study for safety reasons. The investigator believed that the relationship to study drug was "none" and this reviewer agrees.

Patient 012-038: This 66-year-old man with a history of HTN, MI, angioplasty, CABG, lower back pain, BPH, acid reflux, seasonal allergies, and hypercholesterolemia reported an episode of atrial flutter (considered clinically significant) beginning approximately 2 months after starting study drug and lasting for 2 weeks. The last dose of study drug preceding the event was taken 3 days prior. The patient reported an adverse event of SOB on 24 Aug 2000; he went to his cardiologist who diagnosed atrial flutter after a treadmill test was performed. Study drug was discontinued temporarily while the patient's condition was stabilized with Toprol (metoprolol), Cardizem CD (diltiazem), and Cordarone (amiodarone). The investigator received permission from Bayer to restart study drug. Electrocardiographic findings were fairly consistent throughout the study and included, IVCD, left anterior hemiblock, nonspecific ST/T wave abnormalities, and poor R-wave progression. Sinus rhythm was either normal or slightly bradycardic at all

ECGs during the study. The patient completed the study. The investigator rated the relationship to study drug as "none" and the reviewer believes that the relationship is "unlikely."

This 55-year-old man with a history of headaches and a cholecystectomy, discontinued study drug after approximately 2-1/2 months due to tachycardia. Electrocardiographic findings showed sinus rhythm (rate 115 bpm), with no atrial fibrillation or atrial flutter. At his early termination visit, his blood pressure was also elevated, and hypertension was added as an adverse event. The only medication the patient took during the study was Tylenol (acetaminophen). Listed below are the patient's blood pressures and heart rates during the study.

	Supine BP (mmHg)	**Standing BP (mmHg)**	**Supine HR (bpm)**	**Standing HR (bpm)**
Visit 1 (24 May 2000)	152/107	151/113	88	96
Visit 2 (28 Jun 2000)	154/90	152/88	88	100
Visit 3 (26 Jul 2000)	155/99	155/100	119	140
Visit 4 (18 Aug 2000)	151/98	142/94	106	125
Visit 5 (20 Sep 2000)	174/112	171/116	121	143

The patient was advised to follow up with his primary care physician. The investigator rated the relationship to study drug as "not assessable." The reviewer can not explain the reason for the tachycardia but believes the relationship is possible.

Patient 022-031: This 52-year-old man with a history of non-cardiac chest pain, irritable bowel syndrome, hemorrhoids, eczema, anxiety delusional disorder and manic depression reported a 3-week period of chest pain, beginning approximately 4-1/2 months after starting study drug and 2 days after last ingestion of study drug. The event was considered a clinically significant event. All ECGs during the study were within normal limits, with the exception of the Visit 5 ECG (01 Sep 2000) which noted sinus arrhythmia and left atrial abnormality. The chest pain resolved, and the patient completed the study. The investigator rated the relationship to study drug as "probable." The reviewer believes the relationship is "possible."

Patient 024-039: This patient reported as having an arrhythmia had an arrhythmia at randomization and never received study drug.

Patient 095-016: This 69-year-old man with a history of HTN, CABG, and hypercholesterolemia reported clinically significant adverse events of tachycardia and arrhythmia occurring approximately 4 months after starting study drug and 1 day after the last preceding dose. Both events resolved within 8 days. The patient was prescribed atenolol, Coumadin (warfarin), and aspirin and was referred to a cardiologist for a consult. The cardiologist confirmed the presence of atrial fibrillation. ECG findings during the study included first degree AV block, left atrial abnormality, and nonspecific ST changes. Atrial flutter was noted as a finding at the Visit 5 and Visit 7 ECGs

(16 Oct 2000 and 15 Jan 2001, respectively). The patient completed the study. The investigator believed the relationship to study drug was "probable." The reviewer believes it is "possible."

Patient 909-007: This 55-year-old man with a history of hypertension, hypercholesterolemia, left varicocele, penile phlebolith, and trembling in his hands experienced a single episode of hypotension while in the clinic for PK analysis at Visit 3. The patient's supine BP was 86/67 mmHg, and his standing BP was 124/82 mmHg. All other BP measurements taken during the study were consistently between 120-144 mmHg (systolic) and 68-84 mmHg (diastolic). HR ranged from 48-58 bpm throughout the study. The patient completed the study. The investigator rated the relationship to the event as "possible" and the reviewer agrees.

A.8.6 Changes in laboratory values:

No specific trends for changes in laboratory values were identified. Abnormally high ALT was slightly more common in the vardenafil 10 mg (but not the 20 mg) group than in the placebo group. The rates of abnormally high CK were similar for the placebo and vardenafil 10 and 20 mg groups, but higher for the vardenafil 5 mg than for the placebo group. The incidence of high CK in each of the treatment groups is shown in Table 6.

Table 6. Incidence of high CK (safety population)

	Placebo	Vardenafil 5 mg	Vardenafil 10 mg	Vardenafil 20 mg
High CK (%)	23/122 (19%)	37/138 (27%)	33/148 (22%)	29/138 (21%)

In most cases, the CK values did not exceed 3 x ULN. CK exceeding 5 X ULN was more frequent in the placebo than in the drug groups. The 2 cases where CK exceeded 10 x ULN were one each on placebo and on vardenafil 10 mg.

A.8.7 Vital Signs: The change from baseline in supine heart rate was –0.8 for placebo, 3.1 for 5 mg vardenafil, 1.3 for 10 mg vardenafil, and 1.1 for 20 mg vardenafil. The change from baseline in standing systolic blood pressure from baseline (mmHg) was –0.4 for placebo, -3.5 for 5 mg vardenafil, -5.8 for 10 mg vardenafil, and –6.5 for 20 mg vardenafil.

A.9 Reviewer's assessment of efficacy and safety: In the opinion of this reviewer, the efficacy and safety data presented in Trial 100249 support the approval of vardenafil for the treatment of erectile dysfunction.

Appendix B – Clinical Trial 10128 ("A randomized, double-blind, placebo-and active (Viagra) – controlled, multicenter, fixed-dose, parallel group study to investigate the efficacy and safety of the phosphodiesterase Type 5 inhibitor BAY 38-9456 in men with erectile dysfunction") (Trial start: May 24, 2000; Trial completion: January 12, 2001) (The safety data is interim).

B.1 Objectives: The objective of this study was to assess the efficacy and safety of the phosphodiesterase inhibitor vardenafil, tested for 3 months at 3 doses versus placebo, in men with erectile dysfunction. A secondary comparison versus 50 mg sldenafil was also performed. In addition, population pharmacokinetics were assessed.

B.2 Design and conduct summary: This trial was a randomized, double-blind, placebo and active-controlled, multicenter (48 sites in 7 European countries), fixed-dose, five-arm, parallel-group comparison study of placebo, vardenafil 5, 10, and 20 mg, and sildenafil 50 mg in men with erectile dysfunction for more than 6 months. The study consisted of 3 phases: 1) baseline period: 4 weeks without treatment 2) a 12-week, double-blind treatment period and 3) follow-up phase: a 7-day follow-up period to collect data concerning SAE's and a 30-day follow-up from the date of the last dose to capture data concerning the occurrence of death. Of the 845 patients randomized, the placebo, vardenafil 5, 10, and 20 mg groups, and sildenafil 50 mg groups were comprised of 168, 169, 169, 171, and 168 patients, respectively. There were 3 primary efficacy endpoints: 1) erectile function domain of the IIEF calculated as the sum of scores from Questions 1-5 and 15 at Week 12 using LOCF 2) success in penetration ("Were you able to insert your penis into your partner's vagina?") from randomization to Week 12 using overall success rate and 3) success in maintaining erection during intercourse ("Did your erection last long enough for you to have successful intercourse?") from randomization to Week 12 using overall success rate.

Patients were seen at Week –4 (screening), 0 (randomization), and 4, 8, and 12. IIEF and diary data were collected at each visit beginning at Week 0. Vital signs were determined at each visit. Hematology and chemistry values were determined at each visit except Week 8. A 12-lead EKG was performed at screening and at each visit except Week 8. Fasting cholesterol and triglycerides were collected at Weeks 0 and 12. Blood for population PK studies was drawn at Weeks 4 and 8.

B.3 Study population: The study population was men aged 18 years or greater with at least a 6 month history of erectile dysfunction. The baseline characteristics of the study population are shown in Table 1.

Table 1. Baseline characteristics of randomized patients.

	Placebo	Vardenafil 5 mg	Vardenafil 10 mg	Vardenafil 20 mg	Sildenafil 50 mg
Race % Caucasian	68%	66%	68%	67%	68%
Age (years)	55.4	54.6	53.9	54.7	55.2
EF domain of IIEF	13.01	13.19	13.05	13.25	13.33
"Insert penis into partners vagina?" (mean of per-patient % "yes")	41.72	47.80	43.92	43.77	45.81
"Erection long enough for successful intercourse? " (mean of per-patient % "yes")	15.91	14.60	15.95	15.31	16.59

Four hundred seventy-one (59%) of the study population had previously used sildenafil. Of these patients, 351 (75%) had noted an improvement in erections while 119 (25%) had not noted an improvement in erections.

B.4 Inclusion and exclusion criteria: Inclusion criteria included: 1) men with erectile dysfunction for more than 6 months 2) 18 years of age and older and 3) at least 4 attempts at intercourse on 4 separate days during the untreated baseline period, and at least 50% of attempts during this period must be unsuccessful, that is, failed penetration or maintenance of an erection. Exclusion criteria included: 1) penile anatomical abnormalities 2) erectile dysfunction after spinal cord injury 3) history of radical prostatectomy 4) retinitis pigmentosa 5) history of positive test for hepatitis B or C 6) unstable angina 7) history of myocardial infarction, stroke, EKG evidence of ischemia, or life-threatening arrhythmia within prior 6 months 8).atrial tachyarrhythmia with a heart rate of > 100 bpm at screening 9) chronic liver disease or liver function abnormalities (ALT or AST > 3 x ULN) 10) clinically significant hematologic disease or bleeding disorder 11) significant peptic ulcer disease in prior 12 months 12) resting hypotension (SBP < 90 mmHg) or hypertension (SBP > 170 mmHg or DBP > 110 mmHg) on more than 2 occasions 13) symptomatic postural hypotension in prior 6 months 14) uncontrolled diabetes (Hb A_{1c} > 12%) 15) inadequately treated hypothyroidism or hyperthyroidism 16) history of cancer (other than squamous or basal cell skin cancer) within the past 5 years 17) patients taking nitrates or nitric oxide donors

18) patients taking anticoagulants other than anti-platelet drugs 19) patients taking androgens or anti-androgens 20) use of sildenafil or other therapy for erectile dysfunction with 7 days of Visit 1 21) patients with serum testosterone below lower limit of normal 22) serum creatinine >2.5 mg/dL and 23) history of severe migraine headaches with past 6 months.

B.5 Primary and secondary endpoints: Primary efficacy endpoints: 1) erectile dysfunction domain of the IIEF calculated as the sum of scores from Questions 1-5 and 15 at Week 12 using LOCF 2) Success in penetration ("Were you able to insert your penis into your partner's vagina?") from randomization to Week 12 overall success rate and 3) success in maintaining erection during intercourse ("Did your erection last long enough for you to have successful intercourse?") from randomization to Week 12 overall success rate. Secondary endpoints: 1) EF domain scores of IIEF Questionnaire at Week 12 2) EF domain scores of IIEF Questionnaire at Weeks 4 and 8 as observed and LOCF 3) success in penetration and maintenance from randomization to Week 12 as observed 4) success in penetration and maintenance from randomization to Weeks 4 and 8 as observed and LOCF 5) success in penetration and maintenance between Weeks 8 and 12 as observed and LOCF 6) other IIEF domain scores at Weeks 12 as observed and LOCF 7) scores for Questions 3 and 4 of the IIEF at Weeks 4, 8, and 12 as observed and LOCF 8) scores for other questions on the IIEF at Week 12 as observed and LOCF 9) response on patient's and partner's diary (optional) concerning hardness of erection, overall satisfaction with sexual experience, and ejaculation at Week 12 10) Global Assessment at Week 12 11) Fugl-Meyer Life Satisfaction Checklist at Week 12 and 12) Center for Epidemiologic Studies Depression Scale (CESD) at Week 12.

B.6 Withdrawals, compliance, and protocol violations: Of the 1011 patients screened, 845 were enrolled. A total of 718 (85%) patients completed the study: 140 (83%) in the placebo group, 137 (81%) patients in the vardenafil 5, 10, and 20 mg dose groups and 147 (86%) in the sildenafil 50 mg dose groups. Premature discontinuation was lowest in the vardenafil 10 mg dose group (12%) and highest in the placebo group (17%). No patients were excluded from any analyses as a result of a protocol deviation.

B.7 Efficacy analysis:

The results of the efficacy analysis for the 3 primary endpoints are shown in Table 2.

Table 2. Results for primary efficacy parameters at Week 12 (LOCF-ITT)

	Placebo N=158	Vard 5 mg N=150	Vard 10 mg N=155	Vard 20 mg N=158	Sild 50 mg N=159
EF domain of IIEF					
LS mean baseline	13.01	13.19	13.05	13.25	13.33
LS mean value Wk. 12	13.23	19.76*	20.91*	21.49*	21.27*
Success in penetration at Week 12					
LS mean baseline	41.72	47.80	43.92	43.77	45.81
LS mean value Week 12	45.35	71.75*	76.43*	79.48*	78.74*
Success in maintenance at Week 12					
LS mean baseline	15.91	14.60	15.95	15.31	16.59
LS mean value Week 12	24.95	54.88*	61.58*	63.92*	64.93*

- $p < 0.0001$

The Bonferroni adjustment to the p-values was only made for the comparison of vardenafil with placebo. No adjustment was made for the comparisons with sildenafil or between treatment groups.

Slightly higher erectile domain scores of the IIEF were seen with increasing doses of vardenafil. The p-value for the comparison between 5 mg and 20 mg vardenafil was 0.0388.

B.8 Safety analysis:

B.8.1 Extent of exposure: The mean duration of treatment in the placebo group was 75 days compared to 80, 80, 76, and 78 days in the vardenafil 5, 10, and 20 mg and the sildenafil 50 mg groups respectively. The overall number of doses

per patient week was 1.9 in the placebo group, and 2.2, 2.1, 2.1, and 2.1 in the vardenafil-5, 10, and 20 mg and the sildenafil 50 mg groups, respectively.

B.8.2 Serious adverse events:

Deaths: Two deaths were reported during the trial (one patient had not taken study medication and the other was in the sildenafil group).

The first patient was a 60-year-old-man with a history of diabetes and hypertension. He took study drug (sildenafil) shortly before sexual intercourse and died shortly afterwards. The cause of death was reported as myocardial infarction. The investigator reported that the relationship to study drug (sildenafil) was possible.

The second death was in a patient randomized to vardenafil 10 mg. He did not return to the clinic and was discovered afterwards to have died of bronchogenic carcinoma 45 days after randomization. There was no evidence that any study medication had been taken.

Serious adverse events: There were a total or 25 serious adverse events in the trial: 8 (5%), 1 (<1%), 5 (3%), 5 (3%), and 6 (4%) in the placebo, vardenafil 5, 10, and 20 mg, and sildenafil groups, respectively. These events are shown in Table 3.

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Table 3. Serious adverse events

Treatment	Patient number	Event	Relationship to study drug (investigator)
Placebo	39542	Diabetes	None
	39902	Fem-pop bypass	None
	40268	CVA	None
	40326	Chest pain	Unlikely
	40330	Chest pain	None
	40726	Colon Ca	Not assessable
	40858	Urethral prosthesis	None
	40905	Femur fracture	None
Vardenafil 5 mg	40538	Cholelithiasis	None
Vardenafil 10 mg	39677	Car wreck	None
	40084	Chest pain	Unlikely
	40257	CK value of 18690 U/L	None
			None
	40839	Abdominal hernia	None
	40962	Knee trauma	None
Vardenafil 20 mg	39849	Tachycardia	None
	40765	Vertigo and deaf	None
	40767	Epistaxsis	None
	40911	Diabetes	None
	40976	Hernia	None
Sildenafil 50 mg	39434	Chest pain	Possible
	40276	Hip surgery	None
	40348	Myocardial infarct	Possible
	40396	Elevated CK	Possible
	40748	Increased GGT and ALT	Probable
	40886	Renal failure	None

Patient 40257 (vardenafil 10 mg group) was a 49-year-old-man who had a CPK of 18690 on October 16, 2000. He had a history of back pain for 30 years, history of hepatitis (1976) and urticaria since 1998. He developed a frozen shoulder on September 6, 2000, but this condition resolved in October, 2000. On October 16, 2000, his ALT and AST were 124 U/L (nl=6-43 U/L) and 438 U/L (nl=11-36 U/L), respectively. No EKG changes were seen on several studies. He gave no history of angina but stated that he had acute muscle pain following an excessive work-out in the gym 2 days prior to October 16, 2000. There was no evidence of myoglobinuria or viral illness. On October 23, 2000, his CK was normal at 239 U/L. He had finished taking study drug on October 15, 2000.

Reviewer's comment: The cause of the elevated CK and liver function studies is not clear. It is possible that the CK elevation was secondary to physical exertion.

B.8.3 Discontinuations due to study drug:

The discontinuation rates due to adverse events for the 5 groups of patients are shown in Table 4.

	Placebo N=160	Vardenafil 5 N=157	Varden 10 N=159	Varden 20 N=163	Sildenafil N=164
Discontinuation due to adverse event	3 (1.9%)	1 (0.6%)	2 (1.3%)	9 (5.5%)	6 (4%)

The discontinuation in the vardenafil 5 mg group was due to headache. The two discontinuations in the vardenafil 10 mg group were due to possible myocardial ischemia and abdominal pain. The 9 in the vardenafil 20 mg group were tachycardia, back pain, headache, facial burning, headache, worsened hypertension, vertigo, muscle cramps, and abdominal pain.

Patient 040-036 experienced back and pelvic pain and study drug was discontinued. The investigator described the event as follows: "These events lasted for 24 hours at each time. The back pain was characterized in one area on the right of the back. Pelvic pain occurred on the left side."

B.8.4 Frequent adverse events:

The most frequent drug-related adverse events (incidence of >5%) are shown in Table 5.

Table 5. Incidence of the most frequent drug-related adverse events

	Placebo	Vard 5	Vard 10	Vard 20	Sildenafil
Headache	5 (3%)	15 (10%)	8 (5%)	28 (17%)	17 (10%)
Vasodilation	3 (2%)	12 (8%)	20 (13%)	22 (14%)	18 (11%)
Dyspepsia	1 (<1%)	5 (3%)	5 (3%)	11 (7%)	8 (5%)
Rhinitis	1 (<1%)	1 (<1%)	8 (5%)	10 (6%)	2 (1%)

The incidence of back pain was 5% placebo, 3% vardenafil 5 mg, 1% vardenafil 10 mg, <1% vardenafil 20 mg, and 2% sildenafil 50 mg. The incidence of myalgia was <1% placebo, 1% vardenafil 5 mg, 0% vardenafil 10 mg, <1% vardenafil 20 mg, and 1% sildenafil 50 mg.

B.8.5 Changes in laboratory values:

No specific trends for changes in laboratory values were identified. The incidences of elevated CPK is shown in Table 6.

Table 6. Incidence of elevated CPK

	Placebo	Varden 5 mg	Vard 10 mg	Vard 20 mg	Sild 50 mg
High CPK	28/121	31/116	34/119	42/120	30/120

B.8.7 Vital Signs:

Supine systolic blood pressure increased 0.4, 0.5, 2.1, 0.2, and 1.4 mmHg in the placebo, vardenafil 5, 10, and 20 mg, and sildenafil groups, respectively from baseline. Pulse changes from baseline were 0.5, 0.9, 0.9, 0.2, and –0.7 bpm in the placebo, vardenafil 5, 10, and 20, and sildenafil groups, respectively.

B.9 Reviewer's assessment of efficacy and safety: In the opinion of the reviewer, the efficacy and safety data presented in Trial 10128 support the approval of vardenafil for the treatment of erectile dysfunction.

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Appendix C – Trial 100250 ("A randomized, double-blind, placebo-controlled, multi-center, fixed-dose, parallel group, 3-month comparison study to investigate the efficacy and safety of the phosphodiesterase type V inhibitor BAY 38-9456 in males with erectile dysfunction and diabetes mellitus') (Protocol 100250) (Trial start: 4/7/2000; trial completion 11/7/2000)

C.1 Objective: 1) Assess the efficacy and safety of the phosphodiesterase type V inhibitor vardenafil in the treatment of diabetic men with erectile dysfunction (ED) and 2) determine plasma levels of vardenafil after dosing to perform population pharmacokinetic analysis on the total population of subjects studied in the clinical development program.

C.2 Design and conduct summary: This study was a multicenter (47 sites in the United States and Canada), randomized, double-blind, placebo-controlled, fixed-dose, 3-arm parallel group comparison of vardenafil 10 and 20 mg and placebo in men with erectile dysfunction for more than 6 months and with type 1 or type 2 diabetes mellitus. ED was defined as the inability to achieve or maintain penile erection sufficient for satisfactory sexual performance. The study consisted of 2 phases: 1) baseline: 4 weeks without treatment and 2) placebo-controlled phase:12 weeks of double-blind treatment (vardenafil 10 or 20 mg or placebo).

Of the 736 patients screened, 284 discontinued or were dropped during the 4-week baseline period and 454 were randomized (150 to placebo, 153 to vardenafil 10 mg and 149 to vardenafil 20 mg). Patients were instructed to take study medication about 1 hour before intended sexual intercourse. There were 3 primary efficacy endpoints: 1) erectile function domain score of the IIEF at LOCF 2) success in penetration from randomizaton to Week 12 and 3) success in maintaining erection from randomization to Week 12.

Patients were seen at Week –4 (screening), 0 (randomization), and 4, 8, and 12. IIEF and diary data were collected at Weeks 0, 4, 8, and 12. Hematology, chemistry, and urinalysis were performed at Weeks –4, 0, 4, and 12. Supine and standing vital signs were measured at each visit. A 12-lead EKG was performed at Weeks –4, 0, 4, and 12. Fasting total serum cholesterol and fasting serum triglycerides were obtained at Weeks 0 and 12. Plasma samples were obtained at Week 0 and at Weeks 4 and 12 for determination of population pharmacokinetics. The first blood sample was collected between 15 and 45 minutes and the second between 60 and 180 minutes post-dosing. After completion of this protocol, patients were eligible to be enrolled in extension study 100312.

C.3 Study population: The study population was men aged 18 years or greater with at least a 6 month history of erectile dysfunction. The baseline characteristics of the study population are shown in Table 1.

Table 1. Baseline characteristics of the study population.

	Placebo N=143	Vardenafil 10 mg N=152	Vardenafil 20 mg N=144
Race % Caucasian	79%	82%	78%
Age (years)(mean)	56.8	58.0	56.9
EF domain of IIEF	11.0	10.8	12.0
"Insert penis into partner's vagina?"(mean of per-patient % "yes")	30.3	28.7	37.8
"Erection long enough for successful intercourse?"(mean of per-patient % "yes")	11.0	8.9	14.7

Approximately 80% of the patients were Caucasian, 9% Black, and 8% Hispanic. Approximately 60% of patients had previously used Viagra, which improved erections in nearly all of these patients. None of the patients had stopped Viagra because of side effects.

C.4. Inclusion and exclusion criteria: Inclusion criteria included: 1) men 18 years of age or older with ED 2) clinical diagnosis of type 1 or type 2 diabetes mellitus 3) $HbA_{1c} < 12\%$ 4) at least 4 attempts at sexual intercourse on 4 separate days during the untreated baseline period. At least 50% of these attempts had to have been unsuccessful, that is, failed penetration or maintenance of erection. Exclusion criteria included: 1) penile anatomic abnormalities 2) ED after spinal cord injury 3) history of radical prostatectomy 4) retinitis pigmentosa 5) history of positive test for hepatitis B or C 6) unstable angina 7) history of myocardial infarction, stroke, EKG evidence of ischemia, or life-threatening arrhythmia in the past 6 months 8) uncontrolled atrial tachyarrhythmia at screening (ventricular response > 100 bpm 9) chronic liver disease or AST or ALT > 3 x ULN 10) clinically significant hematologic disease or bleeding disorder 11) significant peptic ulcer disease within past 12 months 12) resting hypotension (SBP < 90 mmHg) or hypertension (SBP > 170 mmHg or DBP > 110 mmHg) 13) symptomatic postural hypotension in past 6 months 14) proliferative diabetic retinopathy that progressed within 6 months before screening 15) autonomic neuropathy associated with clinically significant gastroparesis 16) inadequately treated hyperthyroidism or hypothyroidism 17) history of cancer other than skin squamous or basal cell carcinoma within the past 5 years. 18) nitrates or nitric oxide donors 19) antiandrogens 20) anticoagulants other than anti-platelet drugs 21) androgens 22) trazodone 23) vardenafil before Visit 1 24) sildenafil within 7

days of Visit 1 25) testosterone below lower limits of normal 26) creatinine >2.5 mg/dL 27) history of severe migraine headaches within the past 6 months and 28) history of unresponsiveness or significant side effects to sildenafil.

C.5 Primary and secondary endpoints: Primary efficacy endpoints were: 1) EF domain of the IIEF calculated as the sum of scores from questions 1-5 and 15 at Week 12 using LOCF to account for drop-outs 2) success in penetration ("Were you able to inert your penis into the partner's vagina?") from randomization to Week 12 using LOCF and 3) success in maintaining erection during intercourse ("Did your erection last long enough for you to have successful intercourse?") from randomization to Week 12 using LOCF. Secondary endpoints included: 1) EF domain scores of IIEF at Week 12, as observed 2) EF domain scores of IIEF at Weeks 4 and 8, as observed and LOCF 3) success in penetration and maintenance of erection from randomization to Week 12, as observed 4) success in penetration and maintenance of erection from randomization to Weeks 4 and 8, as observed and LOCF 5) success in penetration and maintenance of erection between Weeks 8 and 12, as observed and LOCF 6) other IIEF domain scores at Week 12, as observed and LOCF 7) scores for questions 3 and 4 of the IIEF at Weeks 4, 8, and 12, as observed and LOCF 8) scores for other questions on the IIEF at Week 12, as observed and LOCF 9) Global Assessment question at Week 12 ("Has the treatment you have been taking over the past 4 weeks improved your erection?"), as observed and LOCF 10) Fugl-Meyer quality of life questionnaire at Week 12 and 11) Center for Epidemiologic Studies Depression Scale at Week 12.

C.6 Withdrawals, compliance, and protocol violations:

Four-hundred fifty-two patients were randomized: 150 to placebo, 153 to vardenafil 10 mg, and 149 to vardenafil 20 mg. Two hundred eighty-four patients discontinued during the 4-week baseline phase, the majority because of protocol violations. Among the 452 randomized patients, 73 discontinued prematurely. Overall, 84% of the randomized patients completed the study (placebo 81%, vardenafil 10 mg 86%, and vardenafil 20 mg 85%). Overall, 11 (2%) patients discontinued because of an adverse event (placebo 2 (1%), vardenafil 10 mg 4 (3%), and vardenafil 20 mg 5 (3%). Approximately 25% of randomized patients had at least one protocol deviation. The majority of these deviations involved taking more than one dose of study medication on a calendar day. Four patients took 3 doses on a calendar and the remainder of the patients took 2 doses.

C.7 Efficacy analysis:

The results of the efficacy analyses for the 3 primary endpoints are shown in Table 2.

Table 2. Results of primary efficacy parameters: IIEF EF domain at LOCF and overall per-patient diary results for penetration and maintenance questions (ITT population)

	Placebo	Vardenafil 10 mg	Vardenafil 20 mg
EF domain of IIEF			
LS mean baseline	11.2	11.9	12.4
LS mean value	12.6	17.1*	19.0*
Success in penetration			
LS mean baseline	33.2	30.9	41.1
LS mean value	36.4	61.2*	63.8*
Success in maintenance			
LS mean baseline	11.3	9.4	15.4
LS mean value	23.0	49.2*	54.2*

- p= 0..0001 (comparison of the vardenafil group with placebo)

The study was designed to compare the efficacy results of the 2 vardenafil doses and placebo, not between vardenafil 10 mg and 20 mg. The difference between the 20 mg and 10 mg groups was statistically significant at LOCF for the EF domain score and numerically better, but not statistically superior, regarding the diary questions.

C.8 Safety analysis:

C.8.1 Extent of exposure: The safety analysis includes 143 patients in the placebo group, 152 in the vardenafil 10 mg group, and 144 in the vardenafil 20 mg group. The mean duration of treatment was approximately 78 days in each treatment group. The mean total number of doses taken were 21.3 for placebo, 24.6 for vardenafil 10 mg, and 24.2 for vardenafil 20 mg. The mean number of doses taken per week was 1.8, 2.1, and 2.0 for the placebo, vardenafil 10 mg and vardenafil 20 mg, respectively.

C.8.2 Serious adverse events:

Deaths: There were no deaths during the study.

Serious adverse events: Serious adverse events occurred in 4 (3%) placebo patients, 3 (2%) vardenafil 10 mg patients, and 4 (3%) vardenafil 20 mg patients. A listing of SAE's is shown in Table 3.

Table 3. SAE's in 3 study groups

Placebo	Vardenafil 10 mg	Vardenafil 20 mg
1) Nausea and chest pain 2) Foot ulcer 3) Rectal bleeding 4) Foot cellulitis	1) Chest pain and ST depression 2) Foot infection 3) Chest pain, SOB, laryngeal edema, and wheezing	1) cystoscopy for hematuria 2) atrial fib and myocardial infarction 3) Amnesia and headache 4) Numbness

Vardenafil 10 mg:

Patient 017-009: 58-year-old man with Type 2 DM experienced intermittent chest pain, shortness of breath, and nausea during the week prior to the end of the study. An EKG at the final visit revealed ST-T depression suggestive of ischemia and coronary artery disease was diagnosed. He was hospitalized and underwent a double-vessel coronary artery bypass graft. He did not enter the extension study due to the possible requirement for nitrates. The relationship to study drug of the chest pain and ST-T segment changes was rated by the investigator as "possible." No information concerning the timing of dosing and the clinical events is provided. Concomitant medications included glyburide, fosinopril, and ibuprofen.

Reviewer's comment: This reviewer believes the relationship to study drug is possible.

Patient 047-005: A 59-year-old experienced 3 episodes each of chest tightness, shortness of breath, laryngeal edema, and wheezing after each of the 3 doses of study drug taken during the trial. The symptoms increased in severity (mild to moderate to severe). The patient was not hospitalized but study drug was discontinued. The investigator rated the relationship to study drug as "probable."

Reviewer's comment: These symptoms are consistent with an allergic reaction to the study drug.

Vardenafil 20 mg:

Patient 024-011: A 64-year-old man with a history of a myocardial infarction, 3 angioplasties, renal insufficiency, and hypertension was hospitalized for atrial fibrillation and chest "pressure." The last dose of study medication was taken 2 days prior to the event. He was medically converted to sinus rhythm. Cardiac enzyme findings were consistent with a non-transmural myocardial infarct. He

completed the study. The investigator rated the relationship to study drug as "unlikely."

Reviewer's comment: Primarily because of the 48 hour time lapse between drug ingestion and symptoms, the reviewer agrees that the relationship to study drug is unlikely.

C.8.3 Discontinuations due to adverse events:

Discontinuation rates for the 3 groups were: placebo 2 (1%), vardenafil 10 mg 4 (3%), and vardenafil 20 mg 5 (3%). The 2 patients in the placebo group discontinued because of abnormal liver function tests and urogenital surgery. In the vardenafil 10 mg group, patient 047-005 is discussed above. Two patients in the vardenafil 10 mg group discontinued because of vasodilation. In the 20 mg vardenafil group, 1 patient discontinued because of vasodilation and 1 (patient 020-007) discontinued because of abnormal vision.

Patient 020-007 was a 55-year-old man who reported "visual disturbances" (?symptoms) via telephone. He did not return for Visit 3 and was lost to follow-up.

C.8.4 Frequent adverse events: Adverse events judged "possibly" or "probably" related to study drug and occurring with an incidence of 5% or higher in one of the vardenafil groups than in the placebo group are shown in Table 4.

Table 4. Drug related adverse events

	Placebo N=143	Vardenafil 10 mg N=152	Vardenafil 20 mg N=144
Headache	3 (2%)	14 (9%)	15 (10%)
Vasodilation	1 (<1%)	13 (9%)	14 (10%)
Rhinitis	0	4 (3%)	8 (6%)
Sinusitis	0	1 (<1%)	2 (1%)

Dyspepsia occurred in 4.9% of the 20 mg group, 3.3% of the 10 mg group, and 2.8% in the placebo group.

Patients aged 65 years and older were not at increased risk of experiencing back pain, dyspepsia, headache, rhinitis, vasodilation, myalgia, or abnormal vision.

C.8.5 Clinically significant events:

The sponsor selected certain cardiovascular and visual events as "clinically significant."

In the placebo group, 4 patients had clinically significant events (visual disturbances in 3 and chest pain in one).

In the vardenafil 10 mg group, 10 patients had clinically significant events (2 of which, hypotension and conjunctivitis, were present prior to treatment with study drug). Study drug was discontinued in one patient (047-005) because of chest pain (discussed above). Events in the other 9 patients were chest pain (3 patients), conjunctivitis (2 patients), hypotension (2 patients), arrhythmia (1 patient), and tachycardia (1 patient).

In the vardenafil 20 mg group, 12 patients had clinically significant events (2 of which, angina and amblyopia, were present prior to treatment). Study drug was discontinued in 1 patient (002-007) because of abnormal vision. In patient 024-011 discussed above, the events (atrial fibrillation and myocardial infarct) were serious and study drug was discontinued. Clinically significant events in the other 10 patients were visual disturbances (photophobia, amblyopia, and conjunctivitis) in 8 patients, angina in 1 patient, and chest pain in 1 patient.

C.8.6 Changes in laboratory values:

Abnormally high serum glucose and CK were each reported at least 5% more often in one of the vardenafil groups relative to the placebo group.

The CK elevations by treatment group are shown in Table 5.

Table 5. CK abnormalities at any time during the study.

	Placebo	Vardenafil 10 mg	Vardenafil 20 mg
Any CK elevation	14/105 (13%)	20/116 (17%)	22/101 (22%)
CK > 3 x ULN	0	1/145 (<1%)	5/138 (4%)
CK > 5 x ULN	0	1/146 (<1%)	0
CK > 10 x ULN	0	0	0

MB isoenzyme was elevated in 6 (2 placebo and 4 vardenafil 20 mg) of 7 patients with treatment-emergent CK elevations to >500 U/L. None of them was symptomatic.

C.8.7 Vital signs:

The changes in vital signs in patients whose pulse and blood pressure were measured (by chance) from 11 minutes to 5 hours of dosing with study drug compared to values obtained at randomization are shown in Table 6.

Table 6. Mean difference in vital signs

	Placebo	Vardenafil 10 mg	Vardenafil 20 mg
Standing HR (bpm)	-0.3	3.0	0.1
Standing SBP (mmHg)	0.3	-2.9	-4.5

C.8.8 QT changes:

QT chages from baseline were examined in the patients whose EKG's (by chance) were recorded within 11 minutes to 5 hours after dosing. These data is presented in Table 7.

Table 7. Mean QT differences

	Placebo N=69	Vardenafil 10 mg N=76	Vardenafil 20 mg N=66
QT interval (ms)	3.2	-2.1	-1.4
QT (Bazett)	6.4	6.8	13.3
QT (Fridericia)	4.1	4.1	8.2

Reviewer's comment: The design of the study does not permit conclusions concerning the effect of vardenafil on the QT interval.

C.9 Reviewer's assessment of efficacy and safety: In the opinion of this reviewer, the efficacy and safety data submitted in Trial 100250 support the approval of vardenafil for the treatment of erectile dysfunction.

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Appendix D – Clinical Trial 100285 ("A randomized, double-blind, placebo-controlled, multicenter, fixed-dose, parallel group, 3-month comparison study to investigate the efficacy and safety of the phosphodiesterase type V inhibitor BAY 38-9456 in males with erectile dysfunction following radical prostatectomy") (Trial start: 7/11/2000; trial completion 6/1/2001)

D.1 Objective: to assess the efficacy and safety of the phosphodiesterase V inhibitor vardenafil in the treatment of men with erectile dysfunction following radical prostatectomy.

D.2 Design and conduct: This study was a multicenter (65 United States and Canadian sites), randomized, double-blind, placebo-controlled, fixed-dose, 3-arm, parallel group comparison of vardenafil 10 mg, 20 mg, and placebo in men with ED following radical prostatectomy. The study consisted of 3 phases: 1) baseline: 4 weeks without treatment of ED 2) treatment: 12 weeks of double-blind treatment (vardenafil 10 or 20 mg or placebo) and 3) 7 days from the date of the last dose in which to collect data concerning SAE's and 30 days from the date of the last dose in which to collect occurrence of death.

Of the 567 patients screened, 127 discontinued or were dropped during the 4-week baseline phase and 440 patients were randomized (145 to placebo, 146 to vardenafil 10 mg, and 149 to vardenafil 20 mg). Patients were instructed to take study medication about 1 hour prior before intended sexual intercourse. There were 3 primary endpoints: 1) erectile function domain of the IIEF at LOCF 2) success in penetration and 3) success in maintaining erection from randomization to Week 12.

Patients were seen at Week –4 (screening), 0 (randomization), and 4, 8, and 12. IIEF and diary data will be collected at each visit beginning at Week 0. Vital signs were determined at each visit. Hematology and chemistry values were obtained at each visit. A 12-lead EKG was obtained at Weeks –4, 0, 4, and 12.

D.3 Study population: The study population was men with erectile dysfunction who had undergone a radical retropubic prostatectomy at least 6 months and not more than 5 years before screening. The prostatectomy had to have been either bilaterally or unilaterally nerve-sparing. The prostate tumor had to be localized with no positive tumor margin. PSA at screening had to be consistent with the absence of residual prostate cancer. The baseline characteristics of the study population are shown in Table 1.

Table 1. Baseline characteristics of randomized patients.

	Placebo N=140	Vardenafil 10 mg N=140	Vardenafil 20 mg N=147
Race % Caucasian	93	99	87
Age (years) (mean)	60.4	60.9	59.8
EF Domain of IIEF	9.2	9.7	9.5
Diary: "Insert your penis into partner's vagina?" Mean of per-cent "yes"	14.6	21.6	18.4
Diary: "Maintained long enough for successful intercourse?" Mean of per-cent "yes"	6.1	7.2	7.1
Gleason score	6	6	6
Neurovascular bundle sparing, % bilateral	71	72	76

Overall, 93% were Caucasian, 5% were Black, and, in addition, there were 4 Asians, 3 Hispanics, and 1 American Indian.

Approximately 80% of patients had previously used sildenafil, which improved erections in nearly all of these patients.

D.4 Inclusion and exclusion criteria: Inclusion criteria included: 1) men with ED 2) radical retropubic prostatectomy at least 6 months and not more than 5 years before screening documented by the surgeon to be bilaterally or unilaterally nerve-sparing. The prostate tumor had to be localized, with no perforation of the capsule and no positive tumor margins. Presence of erectile function sufficient for intercourse before surgery (at least 50% of attempt at sexual intercourse successful) had to be documented. 3) 18 years of age or older 4) at least 4 attempts at sexual intercourse on 4 separate days during the untreated baseline period. At least 50% of the attempts had to have been unsuccessful,,that is, failed to achieve an erection, failed to penetrate, or failed to maintain an erection. 5) PSA at screening consistent with the absence of residual prostate cancer. Exclusion criteria included: 1) penile anatomic abnormalities 2) ED after spinal cord injury 3) history of retinitis pigmentosa 4) history of a positive test for hepatitis B or C 5) unstable angina pectoris 6) history of myocardial infarction, stroke, EKG ischemia, or life-threatening arrhythmia within the prior 6 months 7) uncontrolled tachyarrythmia (eg atrial fibrillation or flutter) at screening 8) severe chronic liver disease or liver function abnormalities (AST or ALT > 3 x ULN) 9) clinically significant hematologic disease or bleeding disorder 10) history of significant peptic ulcer disease with 1

year prior to Visit 1 11) resting hypotension (SBP < 90 mmHg) or hypertension (SBP > 170 mmHg) 12) symptomatic postural hypotension within 6 months of screening 13) inadequately treated hyperthyroidism or hypothyroidism 14) type 1 or type 2 diabetes mellitus 15) history of malignancy other than prostate cancer within the past 5 years 16) Gleason tumor score of 8 or greater 17) taking nitrates or NO donors 18) taking anticoagulants, except for anti-platelet drugs 19) taking androgens, finasteride, trazodone, antiandrogens, or any other neoadjuvant hormone treatment for cancer 20) sildenafil or other therapy for ED within 7 days of Visit 1 21) ketoconazole, itraconazole, or ritonavir 22) serum creatinine > 2.5 mg/dL 23) serum testosterone below the lower limit of normal 24) history of severe migraine headaches within the past 6 months 25) history of unresponsiveness to sildenafil or significant side effects leading to discontinuation of sildenafil and 26) planned or previous radiation therapy or hormone therapy.

D.5 Primary and secondary endpoints:

Primary endpoints: There were 3 primary efficacy endpoints.

1) the Erectile Function Domain of the IIEF calculated as the sum of scores from questions 1-5 and 15 at Week 12 using the LOCF method to account for dropouts.
2) Success in penetration (Were you able to insert your penis into the partner's vagina?") by patient diary from randomization to Week 12 using LOCF.
3) Success in maintaining erection during intercourse ("Did your erection last long enough for you to have successful intercourse?") by patient diary from randomization to Week 12 using LOCF.

Secondary endpoints included: 1) EF Domain scores of the IIEF at Week 12, as observed 2) EF Domain scores of the IIEDF at Weeks 4 and 8, as observed and LOCF 3) success in penetration and maintenance from randomization to Week 12 , as observed 4) success in penetration and maintenance of erection from randomization to Weeks 4 and 8, as observed and LOCF 5) Global Assessment Question at Week 12 ("Has the treatment you have been taking over the past 4 weeks improved your erections?"), as observed and LOCF and 6) the primary endpoints were evaluated in the subgroup of patients who had documented bilateral nerve-sparing prostatectomy.

D.6 Withdrawals, compliance, and protocol violations: In all, 567 patients were screened and 127 patients discontinued or were dropped from the screening phase of the study. Most patients who discontinued during the screening phase did so because of protocol violations. The per-cent of patients who completed the study were: placebo 67%, vardenafil 10 mg 78%, and vardenafil 20 mg 80%. The percent of patients who discontinued because of an adverse event were: placebo <1%, vardenafil 10 mg 3%, and vardenafil 20 mg 3%. Approximately 25% of randomized patients had at least one protocol violation. The most

common violation was taking more than 1 dose of study medication per day. No patients took more than 2 doses on any calendar day.

D.7 Efficacy analysis:

The results of the efficacy analyses for the 3 primary endpoints are shown in Table 2.

Table 2. Results for primary efficacy parameters

	Placebo	Vardenafil 10 mg	Vardenafil 20 mg
ED domain of IIEF			
LS mean baseline	9.1	9.3	9.2
LS mean value	9.2	15.3*	15.3*
Success in penetration (%)			
LS mean baseline	14.2	21.0	18.3
LS mean value	21.8	46.6*	47.5*
Maintenance success (%)			
LS mean baseline	6.0	6.6	7.0
LS mean value	9.9	37.2*	34.2*

- p = 0.0001 (The p value is for the comparison of the vardenafil group with placebo.

The results in the subpopulation who underwent a bilateral nerve-sparing procedure were similar to the results for the entire ITT popoulation.

The IIEF results in the ITT population were similar for vardenafil 10 mg and 20 mg. This was also true for the diary questions. The study was designed to compare the efficacy of the 2 vardenafil doses and placebo, not that of vardenafil 10 and 20 mg.

D.8 Safety analysis:

D.8.1 Extent of exposure: The vardenafil treatment groups had slightly greater mean duration of treatment (74 and 72 days for the vardenafil 10 and 20 mg groups, respectively) than did the placebo group (64 days). The total number of doses taken per patient group (mean) were 16.3, 20.7, and 17.5 for the placebo, vardenafil 10 mg, and vardenafil 20 mg groups, respectively.

D.8.2 Serious adverse events:

Deaths: There were no deaths during the study.

Serious adverse events: Serious adverse events occurred in 1 (<1%) in the placebo group, 3 (2%) in the 10 mg vardenafil group, and 1 (<1%) in the 20 mg vardenafil group. These SAE's are listed in Table 3.

Table 3. Serious adverse events

Placebo	Vardenafil 10 mg	Vardenafil 20 mg
1) wrist fracture 2) heart block	1) hip fracture 2) epididymitis 3) pulmonary embolus	1) ankle fracture

The investigator rated the relationship of study drug to the SAE as "none" in all cases.

D.8.3 Discontinuations due to adverse events:

The discontinuation rates for adverse events were: placebo 1 (<1%), vardenafil 10 mg 5 (4%), and vardenafil 20 mg 4 (3%).

In the 10 mg group, one patient experienced chest pain and "vasodilation," one palpitation and tachycardia, one vasodilation (flushing), one pulmonary embolus, and one headache.

In the 20 mg group, one patient experienced headache and vasodilation, one insomnia, one elevated liver function tests (patient 103029), one vasodilation and tachycardia, and one headache.

Patient 103029 – This 74-year-old man had elevated liver enzymes (3 x ULN) at randomization. The patient received one dose of study medication. Enzymes were repeated, were again elevated, and he was discontinued from the study.

Reviewer's comment: The reviewer believes that there is no relationship to study drug of this patient's elevated liver function studies.

D.8.4 Frequent adverse events:

The incidence of adverse events which were judged possibly or probably related to study drug and for which the rate in one of the vardenafil groups was greater than 5% higher than the rate in the placebo group are shown in Table 4.

Table 4. Incidence of drug related adverse events

	Placebo N=140	Vardenafil 10 mg N=140	Vardenafil 20 mg N=147
Headache	4 (3%)	21 (15%)	31 (21%)
Vasodilation	0	26 (19%)	31 (21%)
Rhinitis	1 (<1%)	11 (8%)	14 (10%)
Sinusitis	0	0	6 (4%)

Patients aged 65 years or older were not at increased risk for these adverse events.

D.8.5 Clinically significant adverse events:

The sponsor selected certain cardiovascular and visual events as "clinically significant." These events occurred in 2 patients in the placebo group, 8 patients in the vardenafil 10 mg group, and 13 patients in the vardenafil 20 mg group. In the 10 mg vardenafil group, one patient had tachycardia (investigator believed it secondary to study drug), one had "chest pressure," 2 had chest pain, one had "red eyes," another had tachycardia, one had sensitivity to light, and one had blurred vision.

In the 20 mg vardenafil group, one patient developed tachycardia, 2 had abnormal vision, one had conjunctivitis, 3 had tachycardia, 3 had chest pain, and 3 had sensitivity to light.

D.8.6 Changes in laboratory values:

There were no abnormally high laboratory findings occurring in at least 5% more patients in one of the vardenafil groups than in the placebo group. CK was elevation was reported in 27% of the placebo group, 13% of the vardenafil 10 mg group, and 24% of the vardenafil 20 mg group. The magnitude of the CK elevations is shown in Table 5.

Table 5. CK elevation

	Placebo	Vardenafil 10 mg	Vardenafil 20 mg
Any CK elevation	29/106 (27%)	15/113 (13%)	28/116 (24%)
CK >3 x ULN	5/132 (4%)	12/132 (2%)	2/145 (1%)
CK >5 x ULN	2/133 (2%)	0	2/145 (1%)
CK > 10 x ULN	1/133 (<1%)	0	0

MB isoenzyme was elevated in 7 of the 12 patients with CK elevations to >500 U/L. None of them had any symptoms suggestive of heart disease and none had EKG changes.

D.8.7 Vital signs:

No clinically significant differences were seen for heart rate or blood pressure. When compared to baseline, the standing heart rate decreased by 1.2 bpm and the standing systolic blood pressure decreased by 2.0 mmHg in the 20 mg vardenafil group.

D.8.8 QT measurement

At LOCF, there was no increase in the QT interval and in the Bazett and Fridericia corrected QT intervals.

D.9 Reviewer's assessment of efficacy and safety: In the opinion of this reviewer, the efficacy and safety data presented in Trial 100285 support the approval of vardenafil for the treatment of erectile dysfunction.

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