Appendix M: Effect of vardenafil on the QT interval

Machine read EKG intervals were obtained in multiple phase 1 and 2 studies. Because of concern expressed by the Committee for Proprietary Medicinal Products (CPMP) that "at present, automatic EKG readings are generally not considered reliable," the sponsor submitted data including manual (computer assisted) readings of EKG data obtained in studies involving both healthy patients and patients with erectile dysfunction. This information is included in Appendix 18.1 of the ISS and is entitled "Supplemental Manual Reading and Statistical Analysis of ECG intervals from Phase I and II Studies." All of the tables reproduced in this appendix are taken from Appendix 18.1 of the ISS.

A summary of the studies is shown in Table 1.

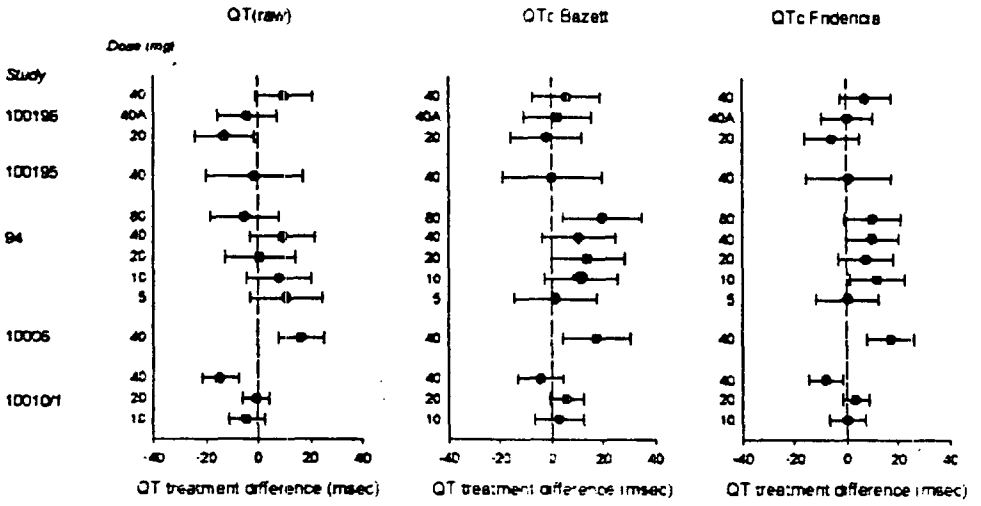
Table 1. Vardenafil studies from which manually read ECG's were obtained.

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.

Raw QT data, 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 and none of the studies was specifically designed as a trial to evaluate the effect of vardenafil on the QT interval.

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

The design and QT data (manually read) from the various trials are discussed below.

<u>The only Trial which evaluated EKG data with the 80 mg dose of vardenafil was Trial 94.</u>

Trial 94 – ("Randomized, double-blind, placebo-controlled, group comparison, dose escalation study to investigate safety, tolerability and pharmacokinetics of BAY 38-9456 after single oral dosing of 5, 10, 20, 40, and 80 mg in young healthy male subjects").

The objective of the study was to investigate the safety and tolerability of BAY 38-9456 after single oral doses. Study drug was BAY 38-9456 solution oral 0.1% (referred to its free base BAY 38-7268). Nine healthy male subjects (aged 18 to 45 years) were enrolled in the 5 mg, 20 mg, and 40 mg dose steps of the study (6 active and 3 placebo in each group). Ten subjects (6 active and 4 placebo) were enrolled in the 10 mg dose group and 8 subjects (5 active and 3 placebo) in the 80 mg group.

There were no serious adverse events. Three patients in the 80 mg group experienced "abnormal vision." One patient in the 80 mg group experienced neck pain rated as "mild." The T_{max} was 0.33 to 2 hours (median 0.625 to 0.75 hours) for all dose steps.

ECG's were performed at 1, 2, 3, 4, 6, 8, 12, and 24 hours after dosing. QT, QTc (Bazett), and QTc (Fridericia) obtained 1 hour after dosing are shown in Tables 2, 3, and 4.

Table 2. QT interval

	Value at visit						Change from baseline at visit					
	N	Mean	Std	Min	Median	Max	N	Mean	Std	Min	Median	Max
Placebo												
Baseline	17	380.7	20.7		377.8		0					
1 HR	17	383.8	20.0		386.7		17	**3.1**	15.8		-0.0	33.3
Bay 38-9456 5mg												
Baseline	5	401.8	24.8		391.1		0					
1 HR	5	410.7	19.7		404.4		5	**8.9**	7.5		13.3	15.6
Bay 38-9456 10mg												
Baseline	6	373.0	16.7		374.4		0					
1 HR	6	385.9	20.1		381.1		6	**13.0**	12.4		13.3	26.7
Bay 38-9456 20mg												
Baseline	6	405.9	15.0		402.2		0					
1 HR	6	403.7	8.6		403.3		6	**-2.2**	9.1		-2.2	8.9
Bay 38-9456 40mg												
Baseline	6	375.2	15.2		378.9		0					
1 HR	6	389.3	19.9		391.1		6	**14.1**	11.6		10.0	35.6
Bay 38-9456 80mg												
Baseline	5	378.7	28.0		375.6		0					
1 HR	5	377.3	28.1		380.0		5	**-1.3**	16.3		0.0	17.8

Table 3. QTc Bazett

	Value at visit						Change from baseline at visit					
	N	Mean		Min	Median	Max	N	Mean	STD	Min	Med	Max
Placebo												
Baseline	17	382.5	18.6		382.2		0					
1 HR	17	379.6	23.7		386.4		17	**-3.0**	16.5		-7.2	
Bay 38-9456 5mg												
Baseline	5	404.2	9.8		401.7		0					
1 HR	5	395.6	9.9		394.6		5	**-8.7**	18.1		-5.1	
Bay 38-9456 10mg												
Baseline	6	373.6	21.2		369.3		0					
1 HR	6	384.9	16.0		385.0		6	**11.4**	10.9		9.0	
Bay 38-9456 20mg												
Baseline	6	387.5	8.4		391.2		0					
1 HR	6	396.9	14.2		389.5		6	**9.4**	12.9		10.0	
Bay 38-9456 40mg												
Baseline	6	387.6	35.4		385.7		0					
1 HR	6	393.6	22.7		389.1		6	**6.1**	21.2		7.8	
Bay 38-9456 80mg												
Baseline	5	391.0	21.5		397.9		0					
1 HR	5	405.1	19.5		407.4		5	**14.0**	12.3		12.8	

Table 4. QTc Friderecia

QTc Interval (Fridericia's) (msec)

	Value at visit						Change from baseline at visit					
Placebo	N	Mean	Std.	Min	Med	Max	N	Mean				
Baseline	17	381.6	11.0		382.6		0					
1 HR	17	380.8	18.8		386.5		17	**-0.8**	12.3	-22.7	-4.3	16.9
Bay 38-9456 5mg												
Baseline	5	403.2	8.4		400.8		0					
1 HR	5	400.5	12.4		393.5		5	**-2.7**	10.7	-17.1	-1.9	10.3
Bay 38-9456 10mg												
Baseline	6	373.2	16.3		372.4		0					
1 HR	6	385.2	14.5		381.4		6	**11.9**	8.2	3.6	10.5	27.3
Bay 38-9456 20mg												
Baseline	6	393.5	9.7		395.5		0					
1 HR	6	399.1	10.5		394.4		6	**5.6**	10.4	-11.1	8.6	15.5
Bay 38-9456 40mg												
Baseline	6	383.1	25.2		381.2		0					
1 HR	6	392.1	20.3		391.5		6	**9.0**	10.8	-3.2	8.8	20.8
Bay 38-9456 80mg												
Baseline	5	386.4	10.5		386.1		0					
1 HR	5	395.2	10.7		394.1		5	**8.8**	4.1	4.4	8.3	15.4

Reviewer's comment: 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. Based on the data from Trial 94, this reviewer is unable to exclude an effect of vardenafil on the QT interval.

In addition to Trial 94, 5 other Trials evaluated the effects of vardenafil 40 mg.

1) **Trial 10006:** ("Randomized, double-blind, placebo-controlled, group comparison, dose escalation study to investigate safety, tolerability, and pharmacokinetics of BAY 38-9456 after multiple oral dosing of 40 mg o.d. and bid for 14 days in young healthy male subjects").

Population and study design: Twelve healthy young men aged 18 to 45 years (mean age 33.4 years) (8 active drug and 4 placebo) participated in each part of the study. Part 1 consisted of patients taking 40 mg daily and Part 2 consisted of patients taking 40 mg bid.

Adverse events:

One patient in Part 1 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. The bilirubin was never elevated. On follow-up, all values returned to the normal range. Ultrasound of the liver was normal. No etiology for the increased transaminases was determined.

Reviewer's comment: In the opinion of this reviewer, vardenafil may have caused the elevated transaminases. No other explanation is available.

During Part 2 of the study, all patients suffered from myalgia and/or back pain from treatment day 2 or 3 onwards. None of the placebo patients 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."

Reviewer's comment: It is not clear how many of the patients with back pain were evaluated.

Symptoms resolved 24 to 48 hours after drug discontinuation. In 7 of the 8 patients the back pain was rated as "moderate." CK values were within normal limits. Further laboratory tests including "virology and immunologic parameters" were unremarkable.

Three patients in the BID dosing group had dizziness (all "mild") and one had postural hypotension ("mild").

Pharmacokinetic data: Following 40 mg oral dosing, the T_{max} was 0.63 hours (range). After the fourteenth dose administration, the T_{max} was 0.50 hours (range

QT data:

The change from baseline in QT/QTc interval with Day 1 predose as covariate at Day 1 Hour 1 is shown in Table 5.

Table 5.

BAY 38-9456/10006 VARDENAFIL STUDY

Table 1.1
Ancova Of Change From Baseline In QT/QTc Interval (msec) With Day 1 Predose As Covariate
Day 1 Hour 1 Population: All Subjects Valid For ECG Analysis

	TREATMENT	LS MEAN	N	COMPARISON	Estimate OF DIFFERENCE	95% Two-Sided Confidence Interval		P-value
DELTA QT (MSEC)	Placebo	-12.76	8	40mg Vs Placebo	16.61	7.72	25.50	0.0009
	Bay38-9456 40mg	3.84	15					
DELTA QTC (BAZETT) (MSEC)	Placebo	-15.00	8	40mg Vs Placebo	17.53	4.64	30.42	0.0102
	Bay38-9456 40mg	2.53	15					
DELTA QTC (FRIDE.) (MSEC)	Placebo	-14.19	8	40mg Vs Placebo	17.25	8.19	26.31	0.0008
	Bay38-9456 40mg	3.06	15					

The summary statistics for QT, QTc Bazett, and QTc Fridericia are shown in tables 6, 7, and 8.

Table 6. QT interval summary statistics.

Summary Statistics of ECG Data
Population: All Subjects Valid for ECG Analysis

QT Interval (msec)

		Value at visit						Change from day 1 predose at visit	
		N	Mean	Std	Min	Median	Max	N	Mean
Placebo									
	Day1 Predose	8	377.2	22.2		376.7		0	
	Day1 1 HR	8	366.7	20.4		364.4		8	**-10.6**
	Day13 Predose	4	363.9	30.0		354.4		4	**-17.8**
	Day13 1 HR	4	371.1	25.3		360.0		4	**-10.6**
Bay 38-9456 40mg									
	Day1 Predose	15	389.9	23.7		391.1		0	
	Day1 1 HR	16	392.2	18.2		391.1		15	**2.7**
	Day13 Predose	7	385.7	27.1		388.9		6	**-10.4**
	Day13 1 HR	7	379.0	23.5		377.8		6	**-17.4**

Table 7. QTc Bazett's summary statistics.

Summary Statistics of ECG Data

Population: All Subjects Valid for ECG Analysis

QTc Interval (Bazett's) (msec)

		Value at visit						Change from day 1 predose at visit	
		N	Mean	Std	Min	Median	Max	N	Mean
Placebo									
	Day1 Predose	8	389.4	15.0		388.9		0	
	Day1 1 HR	8	374.1	11.7		374.2		8	**-15.3**
	Day13 Predose	4	381.1	19.6		383.7		4	**-8.8**
	Day13 1 HR	4	377.0	16.1		376.9		4	**-12.8**
Bay 38-9456 40mg									
	Day1 Predose	15	388.0	23.4		385.7		0	
	Day1 1 HR	16	392.5	23.3		391.2		15	**2.7**
	Day13 Predose	7	384.2	25.2		372.1		6	**-6.8**
	Day13 1 HR	7	383.3	23.0		386.5		6	**-5.9**

Table 8. QTc Fridericia's summary statistics

Summary Statistics of ECG Data

Population: All Subjects Valid for ECG Analysis

QTc Interval (Fridericia's) (msec)

		Value at visit						Change from day 1	
		N	Mean	Std	Min	Median	Max	N	Mean
Placebo									
	Day1 Predose	8	385.1	13.1		381.8		0	
	Day1 1 HR	8	371.5	10.9		372.8		8	**-13.7**
	Day13 Predose	4	375.0	16.4		373.3		4	**-11.9**
	Day13 1 HR	4	374.9	15.4		375.4		4	**-11.9**
Bay 38-9456 40mg									
	Day1 Predose	15	388.4	17.4		389.4		0	
	Day1 1 HR	16	392.2	17.2		393.1		15	**2.8**
	Day13 Predose	7	384.6	23.7		381.8		6	**-7.9**
	Day13 1 HR	7	381.7	19.7		380.8		6	**-9.7**

Reviewer's comment: The change from baseline in both Bazett's and Fridericia's QTc at one hour are 2.7 and 2.8 msec, respectively. The placebo values are negative in the 11 to 13 msec range. The large negative placebo values make interpretation difficult.

2) Trials 10010 and 10011. (Trial 10010 -"Randomized, double-blind, placebo-controlled, 3-fold crossover study in 21 patients with erectile dysfunction to investigate the pharmacodynamics, safety, tolerability, and pharmacokinetics after single dose oral administration of 10 mg or 20mg

BAY-9456") (Trial 10011 was an identical trial which used 20 and 40 mg vardenafil.)

Study design: In Trial 10010, patients received placebo, 10 mg, or 20 mg vardenafil in randomized order in a 3 way cross-over design. In Trial 10011, patients received placebo, 10 mg, and 20 mg vardenafil in randomized order in a 3 way cross-over design. All drug was a solution of the BAY 38-9456 free base.

Men aged 18 to 60 years with erectile dysfunction were recruited for both studies. Twenty-two patients in 10010 and 21 in 10011 were valid for the safety analysis. The mean age in Trial 10010 was 34 years and in 10011 was 44 years. The primary objective of the study was to determine the effect of vardenafil on penile rigidity measured by Rigiscan.

Pharmacokinetics: The Tmax with all three doses of study drug was <1 hour. With the 40 mg dose the Tmax was 0.677 hours with a range of 0.250 to 3.03 hours.

QT data: The first EKG in both studies was obtained 2 ½ hours after dosing. The QT data is shown in Tables 9, 10, 11, and 12.

Table 9.

BAY 38-9456/10010&10011
VARDENAFIL STUDY

TABLE 1.1
Anova Of Change From Predose In QT/QTc Interval (msec) With Predose As Covariate
Hour 2.5
Population: All Subjects Valid For ECG Analysis

	TREATMENT	LS MEAN	N	COMPARISON	ESTIMATE OF DIFFERENCE	95% Two-Sided Confidence Interval LOWER	UPPER	P-value
DELTA QT (MSEC)	Placebo	9.92	44	10mg Vs Placebo	-4.25	-11.26	2.76	0.2310
	Bay38-9456 10mg	5.67	20	20mg Vs Placebo	-0.54	-5.71	4.63	0.8368
	Bay38-9456 20mg	9.38	42	40mg Vs Placebo	-14.40	-21.36	-7.44	0.0001
	Bay38-9456 40mg	-4.48	23	20mg Vs 10mg	3.71	-3.34	10.77	0.2980
				40mg Vs 10mg	-10.15	-19.26	-1.04	0.0295
				40mg Vs 20mg	-13.85	-20.76	-6.96	0.0001
DELTA QTC (BAZETT) (MSEC)	Placebo	-2.09	44	10mg Vs Placebo	3.01	-6.16	12.17	0.5156
	Bay38-9456 10mg	0.92	20	20mg Vs Placebo	6.61	-1.04	12.26	0.0970
	Bay38-9456 20mg	3.52	42	40mg Vs Placebo	-4.43	-12.65	4.03	0.3007
	Bay38-9456 40mg	-6.52	23	20mg Vs 10mg	2.60	-6.19	11.39	0.5571
				40mg Vs 10mg	-7.43	-18.93	4.08	0.2018
				40mg Vs 20mg	-10.04	-18.57	-1.50	0.0218
DELTA QTC (FRIDE.) (MSEC)	Placebo	2.10	44	10mg Vs Placebo	0.38	-6.35	7.12	0.9101
	Bay38-9456 10mg	2.48	20	20mg Vs Placebo	3.44	-1.49	8.38	0.1690
	Bay38-9456 20mg	5.54	42	40mg Vs Placebo	-7.99	-14.43	-1.55	0.0157
	Bay38-9456 40mg	-5.89	23	20mg Vs 10mg	3.06	-3.60	9.72	0.3632
				40mg Vs 10mg	-8.37	-17.11	0.38	0.0600
				40mg Vs 20mg	-11.43	-17.97	-4.89	0.0006

Table 10.

BAY 38-9456/1001081001I
VARDENAFIL STUDY

2BAU001

Table 2
Summary Statistics of ECG Data
Population: All Subjects Valid for ECG Analysis

QT Interval (msec)

		Value at visit					Change from predose value at visit					
		N	Mean	Std	Min	Median	Max	N	Mean	Std	Min	Median	Max
Placebo													
	Predose	44	371.8	25.5		369.8		0					
	2.5 HRS	44	379.4	27.2		382.1		44	7.6	15.7		8.0	
	4 HRS	43	378.8	26.2		388.4		43	6.2	20.5		-8.9	
	6 HRS	44	367.2	22.4		368.1		44	-4.6	18.6		-4.8	
	12 HRS	41	367.7	24.7		370.0		41	-3.1	22.9		-8.4	
	24 HRS	41	373.4	23.9		372.9		41	3.2	16.7		0.0	
Bay 38-9456 10mg													
	Predose	20	369.5	29.6		367.6		0					
	2.5 HRS	21	376.1	28.6		375.1		20	6.6	16.7		6.6	
	4 HRS	21	370.1	32.6		376.3		20	-0.0	25.1		-0.1	
	6 HRS	21	360.0	23.4		357.8		20	-9.4	22.7		-8.1	
	12 HRS	21	366.3	22.4		361.3		20	-3.7	20.9		2.8	
	24 HRS	21	376.6	23.4		373.3		20	7.7	21.1		4.6	
Bay 38-9456 20mg													
	Predose	42	370.7	28.6		374.8		0					
	2.5 HRS	43	379.2	24.9		379.7		42	8.0	17.6		6.7	
	4 HRS	42	365.9	28.5		358.4		42	-4.8	22.5		-6.4	
	6 HRS	42	362.0	23.8		367.6		42	-7.6	18.8		-9.0	
	12 HRS	42	365.6	28.7		358.0		41	-5.6	24.9		-8.0	
	24 HRS	41	366.6	28.1		367.2		40	-4.4	21.9		-8.6	
Bay 38-9456 40mg													
	Predose	28	367.9	26.2		373.0		0					
	2.5 HRS	28	364.4	30.4		367.8		28	-3.5	18.2		-3.3	
	4 HRS	23	356.9	28.6		352.2		23	-11.0	17.6		-11.1	
	6 HRS	23	351.9	31.0		350.0		23	-16.0	18.5		-21.1	
	12 HRS	21	351.8	32.4		357.5		21	-15.8	16.0		-16.9	
	24 HRS	20	353.7	22.7		366.6		20	-14.3	18.5		-11.1	

Table 11.

BAY 38-9456/1001081001I
VARDENAFIL STUDY

2BAU001

Table 2
Summary Statistics of ECG Data
Population: All Subjects Valid for ECG Analysis

QTc Interval (Bazett's) (msec)

		Value at visit					Change from predose value at visit					
		N	Mean	Std	Min	Median	Max	N	Mean	Std	Min	Median	Max
Placebo													
	Predose	44	390.1	20.9		394.6		0					
	2.5 HRS	44	390.6	25.5		397.9		44	0.5	18.8		3.6	
	4 HRS	43	396.7	26.0		394.9		43	7.4	19.7		9.6	
	6 HRS	44	387.5	25.0		396.8		44	7.4	19.6		6.2	
	12 HRS	41	390.8	23.3		394.8		41	1.0	14.4		2.2	
	24 HRS	41	388.3	28.4		385.2		41	-1.5	25.4		-8.4	
Bay 38-9456 10mg													
	Predose	20	400.3	19.8		401.6		0					
	2.5 HRS	21	399.8	25.6		392.4		20	-7.2	18.8		-2.9	
	4 HRS	21	400.5	27.4		396.4		20	-1.8	17.4		-2.6	
	6 HRS	21	405.0	25.1		400.6		20	1.9	14.2		8.4	
	12 HRS	21	403.1	27.6		401.3		20	-1.1	16.6		2.9	
	24 HRS	21	394.4	31.2		389.6		20	-6.8	24.6		0.4	
Bay 38-9456 20mg													
	Predose	42	398.9	28.6		391.4		0					
	2.5 HRS	43	398.5	25.2		395.9		42	1.3	20.2		-0.3	
	4 HRS	43	400.8	32.3		400.2		43	4.2	25.8		9.2	
	6 HRS	43	402.4	29.8		397.4		42	3.4	18.8		2.1	
	12 HRS	42	398.8	28.0		403.8		41	2.0	19.8		5.6	
	24 HRS	41	387.8	29.1		380.8		40	-8.8	23.3		-11.5	
Bay 38-9456 40mg													
	Predose	28	390.7	21.0		386.2		0					
	2.5 HRS	28	387.8	24.3		386.9		23	-2.9	18.0		-8.2	
	4 HRS	23	398.1	22.1		397.3		23	7.4	14.6		9.1	
	6 HRS	23	390.3	24.4		390.0		23	1.5	13.7		-0.1	
	12 HRS	21	391.8	25.9		388.9		21	0.4	15.3		1.2	
	24 HRS	20	381.6	25.8		383.2		20	-7.8	19.8		-8.6	

Table 12.

BAY 38-9456/100108100111
VARDENAFIL STUDY

28AUG01

Table 2
Summary Statistics of ECG Data
Population: All Subjects Valid for ECG Analysis

QTc Interval (Fridericia's) (msec)

	Value at visit						Change from predose value at visit					
	N	Mean	Std	Min	Median	Max	N	Mean	Std	Min	Median	Max
Placebo												
Predose	44	383.6	16.9		383.4		0					
2.5 HRS	44	386.8	21.0		383.8		44	2.9	14.4		3.5	
4 HRS	43	387.5	21.2		385.1		43	4.9	15.8		6.4	
6 HRS	44	386.9	19.7		387.4		44	3.3	13.9		3.2	
12 HRS	41	382.8	20.5		382.7		41	-0.8	12.9		0.3	
24 HRS	41	382.9	21.3		380.8		41	0.1	17.3		-0.9	
Bay 38-9456 10mg												
Predose	20	391.6	18.8		391.6		0					
2.5 HRS	21	389.8	22.6		386.9		20	-1.7	11.1		-0.8	
4 HRS	21	388.7	24.9		383.4		20	-1.1	15.3		1.6	
6 HRS	21	389.1	19.9		386.7		20	-2.2	13.4		-1.4	
12 HRS	21	389.8	22.9		385.0		20	-1.8	11.7		0.3	
24 HRS	21	389.4	24.6		382.7		20	-1.8	14.4		-1.3	
Bay 38-9456 20mg												
Predose	42	387.8	21.7		383.7		0					
2.5 HRS	43	391.7	20.2		390.3		42	3.8	16.3		2.4	
4 HRS	43	388.6	27.8		384.5		42	1.2	19.8		4.1	
6 HRS	43	387.4	24.4		387.0		42	-0.4	14.4		-2.8	
12 HRS	42	386.3	23.1		384.5		41	-1.0	16.5		-0.6	
24 HRS	41	390.3	23.6		390.6		40	-8.0	18.9		-8.6	
Bay 38-9456 40mg												
Predose	23	382.7	17.6		380.1		0					
2.5 HRS	23	378.5	22.2		374.9		23	-8.3	14.4		-2.8	
4 HRS	23	383.8	20.1		382.4		23	0.9	12.3		1.2	
6 HRS	23	378.0	22.3		371.6		23	-4.7	12.6		-5.0	
12 HRS	21	377.8	25.5		378.7		21	5.8	12.8		-5.8	
24 HRS	20	371.9	17.5		375.1		20	-10.0	18.0		-7.1	

Reviewer's comment: The QTc Fridericia value is a negative 3.2 msec at 2.5 hours for the 40 mg dose.

3) **Trial 100195** ("A Randomized, Double-Blind, Placebo Controlled, Parallel Group Trial to Evaluate the Effects of Age and Gender on the Safety, Tolerability and Pharmacokinetics of a Single 40 mg Oral Dose of BAY 38-9456")

Design and patient population: Forty-eight patients were randomly assigned to receive either a single 40 mg dose of BAY 38-9456 or placebo in a ratio of 3:1. Patients were stratified to 1 of 4 groups: 1) 12 men aged 18-45 2) 12 females aged 18-45 3) 12 males aged >65 and 4) 12 females aged >65. EKG's were performed at baseline and at 0.5, 1, 2, 4, and 8 hours post-dose.

Pharmacokinetic data: The T_{max} in all the patient groups was approximately ½ hour.

QT data: The QT data is presented for the men only in Tables 13, 14, 15, 16 and 17.

Table 13.

Table 1.1
Ancova Of Change From Predose In QT/QTc (msec)
With Predose As Covariate--Male Only
Hour 0.5

	TREATMENT	LS MEAN	N	COMPARISON	ESTIMATE OF DIFFERENCE	95% Two-Sided Confidence Interval LOWER	UPPER	P-value
DELTA QT (MSEC)	Placebo	5.98	6	Bay 38-9456 Vs. Plac	-3.15	-19.67	13.38	0.6962
	Bay 38-9456	2.84	18					
DELTA QTC (BAZETT) (MSEC)	Placebo	7.65	6	Bay 38-9456 Vs. Plac	1.79	-19.76	23.35	0.8642
	Bay 38-9456	9.45	18					
DELTA QTC (FRIDE.) (MSEC)	Placebo	5.33	6	Bay 38-9456 Vs. Plac	2.22	-15.61	20.06	0.7979
	Bay 38-9456	7.56	18					

APPEARS THIS WAY
ON ORIGINAL

Table 14.

BAY 38-9456/100195
MED

Table 1.2
Ancova Of Change From Predose In QT/QTc (msec)
With Predose As Covariate--Male Only
Hour 1

	TREATMENT	LS MEAN	N	COMPARISON	ESTIMATE OF DIFFERENCE	95% Two-Sided Confidence Interval LOWER	UPPER	P-value
DELTA QT (MSEC)	Placebo	-0.19	6	Bay 38-9456 Vs. Plac	-1.08	-19.48	17.32	0.9038
	Bay 38-9456	-1.27	18					
DELTA QTC (BAZETT) (MSEC)	Placebo	1.25	6	Bay 38-9456 Vs. Plac	0.17	-18.95	19.29	0.9854
	Bay 38-9456	1.42	18					
DELTA QTC (FRIDE.) (MSEC)	Placebo	-0.27	6	Bay 38-9456 Vs. Plac	1.19	-15.25	17.64	0.8815
	Bay 38-9456	0.92	18					

The summary statistics for QT, QTc Bazett's and QTc Fridericia's are shown below.

Table 15.

BAY 38-9456/100195
MED

29AUG01

Table 2.1
Summary Statistics of ECG Data
Male
Population: All Subjects Valid for Safety

QT Interval (msec)

	Value at visit						Change from predose at visit					
	N	Mean	Std	Min	Median	Max	N	Mean	Std	Min	Median	Max
PLACEBO												
SCREENING	6	382.3	27.4		399.5		0					
PREDOSE	6	372.0	19.6		382.5		0					
30 MIN	6	376.8	19.5		370.0		6	6.8	18.0		9.5	
1 HR	6	376.7	30.7		377.0		6	4.7	17.7		2.0	
2 HRS	6	382.7	24.3		394.5		6	10.7	6.9		13.5	
4 HRS	6	386.0	19.3		395.5		6	14.0	7.3		14.0	
BAY 38-9456												
SCREENING	17	378.0	25.3		378.0		0					
PREDOSE	18	388.9	22.6		382.0		0					
30 MIN	18	391.7	28.2		383.0		18	2.7	18.2		-0.5	
1 HR	18	395.1	18.7		382.0		18	-2.9	19.7		0.5	
2 HRS	18	398.9	25.6		397.0		18	10.0	21.5		6.5	
4 HRS	18	398.0	27.6		392.0		18	7.1	17.3		6.5	

Table 16.

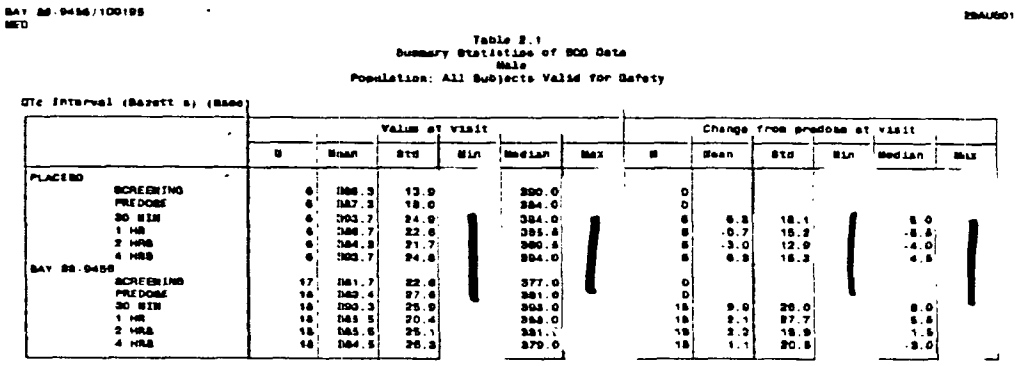
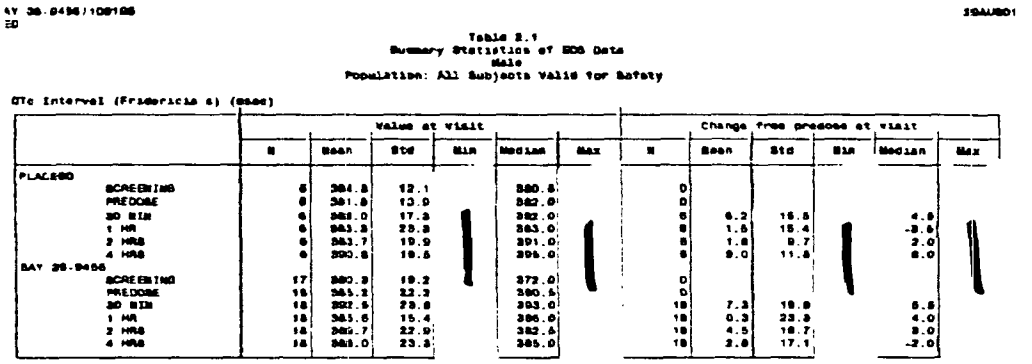


Table 17.



4) **Trial 100196** ("A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Trial to Evaluate the Safety, Tolerability, and Pharmacokinetics of Multiple-Dose Treatments of BAY 38-9456 20 mg and 40 mg Versus Placebo in Healthy Middle-Aged and Elderly Male Subjects")

Design and patient population: Fifty patients were randomized to one of 4 treatment groups: 1) placebo (12 patients) for 31 days 2) 20 mg vardenafil (12 patients) daily for 31 days 3) 40 mg vardenafil (13 patients) every other day alternating with placebo for 31 days and 4) 40 mg vardenafil (13 patients) daily for 31 days. The trial was randomized, double-blind, and placebo controlled. Patients ranged in age from 45 to 70 years.

Adverse events;

Back pain occurred in 3 patients (25%) in the 20 mg group, 3 patients (23%) in the 40 mg every other day group, and in 7 patients (54%) of the 40 mg group.

One patient in the 20 mg group experienced a serious adverse event (atrial fibrillation) and withdrew from the trial. This 66-year-old man had a history of

supraventricular tachycardia. Atrial fibrillation was discovered by the EKG obtained 24 hours after the first dose of study medication and reverted to sinus rhythm approximately 2 hours after the second dose of study medication. He noted symptoms of pressure in the upper back which subsided on conversion to sinus rhythm. CPK drawn shortly after return to sinus rhythm was normal. He had been treated in the past with atenolol for undocumented symptoms of "rapid heart beat." The investigator rated the event as "unlikely" related to study drug.

Reviewer's comment: The episode of atrial fibrillation is temporally related to study drug.

QT data:

On Days 1 and 31, EKG's were performed at pre-dose and at 2, 4, and 8 hours.

Manually read QT data from Trial 100196 are shown in the following 4 tables (18, 19, 20, and 21)

Table 18.

-DAY MULTIPLE DOSE SAFETY & PK IN MALES

Table 1.1
Ancova QT Change From Predose in QT/QTc (msec) With Predose As Covariate
Day1 Hour 2
Population: All Subjects Valid for Safety

	TREATMENT	LS MEAN	N	COMPARISON	ESTIMATE OF DIFFERENCE	95% Two-Sided Confidence Interval LOWER	UPPER	P-value
DELTA QT (MSEC)	PLACEBO	8.96	12	20mg QD Vs. Placebo	-12.80	-24.28	-1.32	0.0296
	20MG QD	-8.65	12	40mg QOD Vs. Placebo	-4.27	-15.44	6.90	0.4454
	40MG QOD	-0.32	13	40mg QD Vs. Placebo	9.98	-1.16	21.13	0.0780
	40MG QD	13.90	13	40mg QOD Vs. 20mg QD	8.53	-2.65	19.71	0.1315
				40mg QD Vs. 20mg QD	22.78	11.86	34.02	0.0002
				40mg QD Vs. 40mg QOD	14.25	3.32	25.19	0.0118
DELTA QTc (BAZETT) (MSEC)	PLACEBO	1.44	12	20mg QD Vs. Placebo	-2.10	-15.82	11.62	0.7569
	20MG QD	-0.67	12	40mg QOD Vs. Placebo	2.27	-10.96	15.50	0.7305
	40MG QOD	8.71	13	40mg QD Vs. Placebo	6.84	-7.25	18.93	0.3736
	40MG QD	7.27	13	40mg QOD Vs. 20mg QD	4.38	-8.56	17.31	0.4967
				40mg QD Vs. 20mg QD	7.94	-5.06	20.94	0.2248
				40mg QD Vs. 40mg QOD	8.68	-9.09	16.21	0.5781
DELTA QTc (FRIDE.) (MSEC)	PLACEBO	2.07	12	20mg QD Vs. Placebo	-5.47	-15.94	5.00	0.2961
	20MG QD	-3.40	12	40mg QOD Vs. Placebo	0.40	-9.61	10.40	0.9366
	40MG QOD	2.47	13	40mg QD Vs. Placebo	7.46	-2.40	17.32	0.1347
	40MG QD	9.53	13	40mg QOD Vs. 20mg QD	5.87	-3.89	15.63	0.2322
				40mg QD Vs. 20mg QD	12.93	3.08	22.79	0.0113
				40mg QD Vs. 40mg QOD	7.06	-2.48	16.60	0.1490

Table 19.

BAY 38-9456/100186
31-DAY MULTIPLE DOSE SAFETY & PK IN SALES

Table 2.1
Summary Statistics of ECG Data

Populations: All Subjects Valid for Safety

QT Interval (msec)

		Value at visit					Change from day one predose at visit				
	N	Mean	Std	Min	Median	Max	N	Mean	Std	Min	Median	Max
PLACEBO												
SCREENING	12	380.9	25.0		378.5		0					
D1 PREDOSE	12	387.6	19.3		386.0		0					
D1 2 HRS	12	391.4	21.0		386.5		12	3.8	15.2		8.0	
D1 4 HRS	12	394.6	20.6		393.0		12	7.0	11.2		8.5	
D31 PREDOSE	11	388.8	20.0		386.0		11	-0.1	11.2		1.0	
D31 2 HRS	11	384.2	18.8		389.0		11	-2.5	15.4		-5.0	
D31 4 HRS	11	394.1	22.1		394.0		11	7.4	13.8		8.0	
BAY 38-9456 200G QD												
SCREENING	12	379.8	25.8		382.5		0					
D1 PREDOSE	12	379.2	16.5		378.5		0					
D1 2 HRS	12	370.5	23.1		375.5		12	-8.7	14.9		-5.5	
D1 4 HRS	12	385.3	24.1		388.5		12	6.1	17.9		8.5	
D31 PREDOSE	11	388.0	26.9		391.0		11	5.2	19.4		6.0	
D31 2 HRS	11	387.1	21.0		394.0		11	7.3	13.6		8.0	
D31 4 HRS	11	396.7	29.8		409.0		11	16.9	20.5		12.0	
BAY 38-9456 400G QOD												
SCREENING	13	384.6	37.1		399.0		0					
D1 PREDOSE	13	384.0	25.3		383.0		0					
D1 2 HRS	13	383.7	37.6		386.0		13	-0.3	9.9		-2.0	
D1 4 HRS	13	396.5	29.8		387.0		13	12.5	13.9		11.0	
D31 PREDOSE	13	388.8	25.7		386.0		13	4.8	16.0		7.0	
D31 2 HRS	13	389.8	25.8		389.0		13	2.8	16.8		8.0	
D31 4 HRS	13	398.6	27.1		396.0		13	14.5	21.0		24.0	
BAY 38-9456 400G QD												
SCREENING	13	394.5	25.5		394.0		0					
D1 PREDOSE	13	385.8	23.1		387.0		0					
D1 2 HRS	13	400.8	27.9		394.0		13	13.8	14.8		18.0	
D1 4 HRS	13	406.0	25.8		408.0		13	18.2	9.8		17.0	
D31 PREDOSE	12	383.4	29.7		385.0		12	-0.3	18.4		-3.0	
D31 2 HRS	12	386.2	21.2		381.5		12	1.5	12.0		0.0	
D31 4 HRS	12	392.8	30.6		384.5		12	8.0	18.8		11.5	

Table 20.

BAY 38-9456/100186
31-DAY MULTIPLE DOSE SAFETY & PK IN SALES

Table 2.1
Summary Statistics of ECG Data

Populations: All Subjects Valid for Safety

QTc Interval (Bazett's) (msec)

		Value at visit					Change from day one predose at visit				
	N	Mean	Std	Min	Median	Max	N	Mean	Std	Min	Median	Max
PLACEBO												
SCREENING	12	397.8	28.6		400.5		0					
D1 PREDOSE	12	397.2	19.7		397.0		0					
D1 2 HRS	12	396.6	27.4		397.5		12	-1.3	15.5		-5.0	
D1 4 HRS	12	395.8	17.2		396.0		12	-1.4	10.5		0.5	
D31 PREDOSE	11	396.7	25.2		396.0		11	0.7	21.0		-2.0	
D31 2 HRS	11	384.5	22.3		385.0		11	-12.5	16.5		-7.0	
D31 4 HRS	11	388.8	24.7		388.0		11	-9.4	18.2		-8.0	
BAY 38-9456 200G QD												
SCREENING	12	386.4	21.7		386.0		0					
D1 PREDOSE	12	380.9	16.8		377.5		0					
D1 2 HRS	12	381.5	18.6		382.5		12	1.9	17.8		8.0	
D1 4 HRS	12	387.4	16.6		391.5		12	7.2	13.2		11.5	
D31 PREDOSE	11	382.5	17.1		383.0		11	1.5	16.5		4.0	
D31 2 HRS	11	388.1	19.4		380.0		11	4.2	22.2		7.0	
D31 4 HRS	11	388.8	23.4		384.0		11	7.8	23.1		2.0	
BAY 38-9456 400G QOD												
SCREENING	13	390.0	14.4		394.0		0					
D1 PREDOSE	13	384.5	17.3		381.0		0					
D1 2 HRS	13	389.0	15.2		382.0		13	4.5	13.1		8.0	
D1 4 HRS	13	399.2	18.9		399.0		13	13.7	14.7		14.0	
D31 PREDOSE	13	378.7	14.2		376.0		13	5.8	14.7		-3.0	
D31 2 HRS	13	387.8	14.4		391.0		13	8.2	16.2		1.0	
D31 4 HRS	13	392.1	20.2		387.0		13	7.5	16.6		0.0	
BAY 38-9456 400G QD												
SCREENING	13	396.7	16.8		396.0		0					
D1 PREDOSE	13	387.5	27.1		382.0		0					
D1 2 HRS	13	394.7	24.0		395.0		13	7.2	13.7		7.0	
D1 4 HRS	13	397.1	27.3		400.0		13	9.6	18.9		13.0	
D31 PREDOSE	12	390.3	22.2		386.5		12	2.7	20.7		8.0	
D31 2 HRS	12	388.1	27.8		379.5		12	-1.8	23.4		1.0	
D31 4 HRS	12	392.1	31.7		380.5		12	5.4	22.2		7.5	

Table 21.

Table 2.1
Summary Statistics of ECG Data

Population: All Subjects Valid for Safety

QTc Interval (Fridericia's) (msec)

	Value at visit						Change from day one predose at visit					
	N	Mean	Std	Min	Median	Max	N	Mean	Std	Min	Median	Max
PLACEBO												
SCREENING	12	395.0	22.5		394.0		0					
D1 PREDOSE	12	393.9	15.2		397.5		0					
D1 2 HRS	12	394.3	21.6		392.5		12	0.4	10.7		-5.0	
D1 4 HRS	12	395.2	16.5		398.0		12	1.3	8.6		2.5	
D31 PREDOSE	11	394.5	22.3		397.0		11	0.5	13.8		0.0	
D31 2 HRS	11	384.8	17.2		385.0		11	-9.9	10.1		-12.0	
D31 4 HRS	11	390.3	21.6		396.0		11	-3.9	12.4		-2.0	
BAY 38-9456 20MG QD												
SCREENING	12	385.3	19.4		384.0		0					
D1 PREDOSE	12	379.8	13.6		380.0		0					
D1 2 HRS	12	377.8	16.5		376.5		13	-2.1	14.4		2.5	
D1 4 HRS	12	386.7	16.5		387.0		12	6.8	11.7		5.0	
D31 PREDOSE	11	382.9	15.6		385.0		11	2.4	10.8		4.0	
D31 2 HRS	11	385.8	16.0		386.0		11	5.3	14.5		8.0	
D31 4 HRS	11	390.9	16.5		393.0		11	10.4	16.9		8.0	
BAY 38-9456 40MG QOD												
SCREENING	13	387.9	16.4		389.0		0					
D1 PREDOSE	13	383.9	9.8		386.0		0					
D1 2 HRS	13	386.5	7.9		387.0		13	2.9	7.3		2.0	
D1 4 HRS	13	397.2	11.1		396.0		13	13.3	10.3		14.0	
D31 PREDOSE	13	381.6	8.8		383.0		13	-2.3	11.5		-2.0	
D31 2 HRS	13	387.2	9.7		388.0		13	3.3	12.9		-2.0	
D31 4 HRS	13	393.9	14.9		392.0		13	10.0	16.0		10.0	
BAY 38-9456 40MG QD												
SCREENING	13	396.1	15.9		395.0		0					
D1 PREDOSE	13	386.8	19.2		389.0		0					
D1 2 HRS	13	396.2	16.4		391.0		13	9.4	15.3		8.0	
D1 4 HRS	13	399.8	21.6		402.0		13	12.8	9.7		14.0	
D31 PREDOSE	12	384.8	15.6		383.0		12	1.6	17.9		7.5	
D31 2 HRS	12	384.9	16.1		381.5		12	-0.3	16.5		-1.0	
D31 4 HRS	12	391.8	11.9		394.5		12	6.4	14.8		8.0	

Reviewer's comment: In the opinion of this reviewer, Trial 100196 does not exclude an effect of vardenafil on the QT interval. QTc Fridericia values increase with increasing doses of vardenafil.

Two trials using 20 mg vardenafil are potentially useful for determining an effect of vardenafil on the QT interval because of the high vardenafil Cmax levels obtained with the concomitant use of CYP 3A4 inhibitors (ketoconazole in Trial 10229 and erythromycin in Trial 10104).

These two trials are reviewed in Appendix J. Manually read QT data for these two trials is also included in ISS Appendix 18.1. **Neither of these trials included a placebo control group.**

QT data from the ISS Appendix 18.1 for Trial 10229 are shown below.

Table 22.

BAY 38-9456/10229
VARDENAFIL STUDY

Table 1
- Analysis of Change From Predose in QT/QTc Interval (msec) With Predose As Covariate
Hour 1
Population: All Subjects Valid for ECG Analysis

	TREATMENT	LS MEAN	N	COMPARISON	ESTIMATE OF DIFFERENCE	95% Two-Sided Confidence Interval LOWER	UPPER	P-value
DELTA QT (MSEC)	Vard 20mg	1.46	12	Sag-Keto Vs 20mg	-0.87	-14.70	12.96	0.8886
	Vard 5mg-Keto.	0.58	12					
DELTA QTC (BAZETT) (MSEC)	Vard 20mg	8.35	12	Sag-Keto Vs 20mg	12.42	-8.46	33.32	0.2117
	Vard 5mg-Keto.	18.77	12					
DELTA QTC (FRIDE.) (MSEC)	Vard 20mg	5.02	12	Sag-Keto Vs 20mg	6.73	-8.42	19.86	0.3848
	Vard 5mg-Keto.	11.83	12					

Table 23.

BAY 38-9456/10229
VARDENAFIL STUDY

Table 2
Summary Statistics of ECG Data
Population: All Subjects Valid for ECG Analysis

QT Interval (msec)

	Value at visit						Change from predose value at visit					
	N	Mean	Std	Min	Median	Max	N	Mean	Std	Min	Median	Max
Bay 38-9456 20mg												
Screening	12	386.7	29.6		381.1		0					
Predose	12	404.4	27.8		406.0		0					
1 HR	12	404.8	26.3		406.7		12	0.4	12.7		-1.1	
Bay 38-9456 5mg-Ketoconazole												
Screening	12	386.7	29.8		381.1		0					
Predose	12	381.7	20.4		381.1		0					
1 HR	12	383.8	16.2		380.0		12	1.7	11.8		1.1	

Table 24.

BAY 38-9456/10229
VARDENAFIL STUDY

Table 2
Summary Statistics of ECG Data
Population: All Subjects Valid for ECG Analysis

QTc Interval (Bazett's) (msec)

	Value at visit						Change from predose value at visit					
	N	Mean	Std	Min	Median	Max	N	Mean	Std	Min	Median	Max
Bay 38-9456 20mg												
Screening	12	390.3	24.1		395.6		0					
Predose	12	384.4	13.2		386.0		0					
1 HR	12	391.3	16.6		391.0		12	6.9	15.7		9.7	
Bay 38-9456 5mg-Ketoconazole												
Screening	12	390.3	24.1		395.6		0					
Predose	12	395.7	26.3		393.8		0					
1 HR	12	403.8	18.6		399.2		12	18.8	26.4		12.4	

Table 25.

BAY 38-9456/10229
VARDENAFIL STUDY

Table 2
Summary Statistics of ECG Data
Population: All Subjects Valid for ECG Analysis

QTc Interval (Fridericia s) (msec)

	Value at visit						Change from predose value at visit					
	N	Mean	Std	Min	Median	Max	N	Mean	Std	Min	Median	Max
Bay 38-9456 20mg												
Screening	12	388.5	14.8		380.8		0					
Predose	12	390.8	14.7		389.9		0					
1 HR	12	395.5	14.3		389.9		12	4.8	10.9		4.8	
Bay 38-9456 4mg-Ketoconazole												
Screening	12	386.5	14.8		380.2		0					
Predose	12	387.4	15.9		390.9		0					
1 HR	12	400.2	14.8		398.6		12	12.8	17.6		12.8	

QT data from ISS Appendix 18.1 for Trial 10104 is shown below.

Table 26.

BAY 38-9456/10104
VARDENAFIL STUDY

Table 1
Anova of Change From Predose in QT/QTc Interval (msec) With Predose As Covariate
Hour 1
Population: All Subjects Valid For ECG Analysis

	TREATMENT	LS MEAN	N	COMPARISON	ESTIMATE OF DIFFERENCE	95% Two-Sided Confidence Interval LOWER	UPPER	P-value
DELTA QT (MSEC)	Vard 20mg	8.11	12	4mg-Eryth vs 20mg	-2.88	-11.10	5.34	0.4484
	Vard 4mg-Eryth	0.21	12					
DELTA QTC (BAZETT) (MSEC)	Vard 20mg	10.21	12	4mg-Eryth vs 20mg	-6.75	-22.03	11.18	0.4807
	Vard 4mg-Eryth	7.46	12					
DELTA QTC (FRIDE.) (MSEC)	Vard 20mg	0.32	12	4mg-Eryth vs 20mg	-3.08	-16.34	10.28	0.6164
	Vard 4mg-Eryth	0.16	12					

Table 27.

VARDENAFIL STUDY

Table 2
Summary Statistics of ECG Data
Population: All Subjects Valid for ECG Analysis

QT Interval (msec)

	Value at visit						Change from predose value at visit					
	N	Mean	Std	Min	Median	Max	N	Mean	Std	Min	Median	Max
Bay 38-9456 20mg												
Screening	12	386.1	30.6		398.8		0					
Predose	12	396.7	39.7		406.7		0					
1 HR	12	400.9	27.3		407.8		12	4.2	6.6		8.2	
Bay 38-9456 4mg-Erythromycin												
Screening	12	386.1	30.9		398.9		0					
Predose	12	400.9	26.3		391.1		0					
1 HR	12	400.0	25.8		398.7		12	-0.9	13.2		1.1	

Table 28.

Table 2
Summary Statistics of ECG Data
Population: All Subjects Valid for ECG Analysis

QTc Interval (Bazett's) (msec)

	Value at visit						Change from predose value at visit					
	N	Mean	Std	Min	Median	Max	N	Mean	Std	Min	Median	Max
Bay 38-9456 20mg												
Screening	12	381.5	15.1	[redacted]	383.2	[redacted]	0			[redacted]		[redacted]
Predose	12	380.3	16.0		383.3		0					
1 HR	12	396.2	14.6		402.4		12	14.9	12.8		17.5	
Bay 38-9456 5mg-Erythromycin												
Screening	12	381.8	15.1		383.2		0					
Predose	12	384.0	18.8		387.8		0					
1 HR	12	391.8	20.3		387.8		12	5.8	17.0		0.1	

BAY 38-9456/10104
VARDENAFIL STUDY
28AUG01

Table 2
Summary Statistics of ECG Data
Population: All Subjects Valid for ECG Analysis

QTc Interval (Fridericia's) (msec)

	Value at visit						Change from predose value at visit					
	N	Mean	Std	Min	Median	Max	N	Mean	Std	Min	Median	Max
Bay 38-9456 20mg												
Screening	12	382.9	16.4	[redacted]	381.4	[redacted]	0			[redacted]		[redacted]
Predose	12	385.4	15.7		385.3		0					
1 HR	12	396.9	14.7		395.1		12	11.5	9.8		12.5	
Bay 38-9456 5mg-Erythromycin												
Screening	12	382.9	16.4		381.4		0					
Predose	12	390.7	17.6		388.9		0					
1 HR	12	394.6	19.8		390.3		12	3.9	14.6		1.3	

Summary:

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 #10104) 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.

In summary, this reviewer is unable to exclude an effect of 40mg vardenafil on the QT interval in Trials 94 and 10196.

Conclusion:

This reviewer is unable to exclude a vardenafil effect on the QT interval at doses of 40 and 80 mg.

APPEARS THIS WAY
ON ORIGINAL

Appendix N – Effect of vardenafil on liver function tests and CK

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 1.

Table 1. 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 2.

Table 2. 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	16/746 (2.1%)	50/1745 (2.9%)
	>5xULN	8/752 (1.1%)	18/1762 (1.0%)
	>10xULN	2/753 (0.3%)	5/1764 (0.3%)
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

The vardenafil treatment group had a slightly higher incidence (2.9%) for CK > 3X ULN compared to placebo (2.1%). In no cases of CK elevation greater than 3X ULN was the CK-MB fraction >2.5% of the total CK. Myalgia was reported by 12/1812 (0.7%) of the vardenafil patients compared to 2/993 (0.3%) of placebo patients. Two patients in the vardenafil group experienced AST elevations >10X ULN.

In the placebo controlled trials (Pool 3), for patients with potentially clinically significant elevated CK values, one placebo patient and one vardenafil 5 mg patient (100249-004-058) also had adverse events of myocardial ischemia during the study. Patient (100249-044-058) was a 53-year-old man, with a history of hypertension and hypercholesterolemia, was randomized to vardenafil 5 mg on June 9, 2000. On August 28, 2000, he had an ECG finding of ST-T wave abnormalities suggestive of anterior ischemia on theVisit 5 ECG. An in-clinic dose of study drug for PK evaluation was given on this date. The anterior ischemia by ECG was reported as an adverse event. No other associated symptoms were noted. A repeat ECG was done on September 6, 2000, and the finding was confirmed. However, at the final visit in the study (December 7, 2000), the ischemic finding was not noted. Additionally, the patient had elevated CK values throughout the study and his concomitant medications included pravastatin. (CK values ranged from 318 to 874 U/L; normal value 18-198 U/L.) On September 13, 2000, the patient saw his primary care physician who determined that the ECG findings and elevated CK values were "normal for this patient."

Adverse events related to chemistry laboratory abnormalities

Table 3 shows all abnormal chemistry laboratory values which were considered by the investigator to be adverse events in Safety Pool 3.

Table 3. Adverse events related to abnormal chemistry laboratory values

	Placebo N=793	Vardenafil N=1812
LFT abnormal	7 (0.9%)	15 (0.8%)
Bilirubinemia	0	1 (<1%)
CK increased	9 (1.1%)	36 (2.0%)

Serious adverse events related to abnormal chemistry values are shown in Table 4.

Table 4. Serious adverse events related to abnormal chemistry values (Safety Pool 3).

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

The serious adverse event involving CK was patient 040257. 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 sponsor believes that the increased CK experienced by this patient had "a clear alternative explanation (excessive exercise) as a probable explanation." This reviewer believes that this explanation is plausible.

Two serious adverse events related to liver function tests occurred in Safety Pool 3.

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

Patient 10232-004-0030 was a 62-year-old Asian male with a history of concurrent diseases of hypertension, hypercholesterolemia, diabetes, hyperuricemia, hypokalemia, and fluid retention, and was described as having a history of alcohol problems when he was enrolled in the study. An adverse event of increased liver enzymes was diagnosed on Day 82 of the study. Laboratory results showed elevated levels of ALT and AST on Day 82 of 62 and 105 U/L (ULN = 43 and 36 U/l, respectively). Screening levels were 16 and 30. The patient did not have any history of viral illness, cirrhosis, or other "liver function disorders." The investigator believed that the increase in liver enzymes was likely related to the patient's alcohol consumption.

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

Adverse events related to abnormal chemistry values that led to premature discontinuation are shown in Table 5 (Safety Pool 3).

Table 5.

Table 8-16 Pool 3: Adverse Events Related to Abnormal Chemistry Lab Values That Led to Premature Discontinuation.

Event	Placebo n=793	Vardenafil n=1812
LFT abnormal	2 (0.3%)	4 (0.2%)
CK increased	1 (0.1%)	0 (0.0%)

Pool 3 Table 2/1.9

Incidence of treatment emergent potentially clinically significant chemistry laboratory abnormalities by dose (Safety Pool 1 – Trials 100249 and 10128) are shown in Table 6.

Table 6.

Table 8-17 Pool 1: Incidence Rates (%) of Treatment-Emergent Potentially Clinically Significant Chemistry Lab Abnormalities* by Dose

Lab Variable	Placebo (%)	Vardenafil 5 mg (%)	10 mg (%)	20 mg (%)
	n = 342	n = 350	n = 358	n = 351
CK > 3*ULN	3.1	3.6	4.6	2.7
>5*ULN	1.9	0.6	2.6	0.6
>10*ULN	0.3	0.0	0.9	0.3
AST >3*ULN	0.3	0.0	0.9	0.3
>5*ULN	0.3	0.0	0.6	0.0
>10*ULN	0.0	0.0	0.6	0.0
ALT >3*ULN	1.6	0.0	0.6	0.3
>5*ULN	0.3	0.0	0.3	0.0
>10*ULN	0.0	0.0	0.0	0.0

* Patients valid for safety

Pool 1, Table 3/3

Individual cases of serious adverse events of increased liver function tests and elevated CK were also evaluated in safety extension Trials 10125 and 10152.

Trial 10125:

Patient 105258: This was a 44-year-old man with a history of hypertension (since 1978) and sinusitis (since 1970). He had a right knee repair in 1978 and experienced depression from 1997 to 1998. During the study he was taking wellbutrin (bupropion), lotrel (amlodipine and benazepril), and a multivitamin. He took dimetapp (bromphenerimine and phenylpropanolamine) for cough for 5 days during March 2001. At screening, safety laboratory tests did not reveal any significantly abnormal values. Particularly, all LFTs were within normal ranges. The patient's medical history did not include any previous liver disorder or reported abnormalities in LFTs. On 10 Jul 2001 (8 days after the last dose of study drug), safety laboratory tests conducted as part of the last visit revealed GGT (207 U/L; normal range up to 61 U/L), ALT (545 U/L; normal range up to 43 U/L) and AST (213 U/L; normal range up to 36 U/L) to be elevated. These elevated values were not associated with any clinical signs or symptoms. Total bilirubin and alkaline phosphatase were within the normal range. No

bilirubinuria was detected by means of dip-stick testing. Laboratory values were repeated 7 days later for confirmation: GGT=244 U/L, ALT=407 U/L, AST=118 U/L. One month later (10 Aug 2001), follow-up tests were done and continued to show abnormalities (GGT=310 U/L, ALT=140 U/L, AST=66 U/L and total bilirubin=1.5 mg/dl (normal=0.2-1.2 mg/dL). The sponsor believes this pattern of laboratory data could indicate hepatitis. However, with the lack of elevation of alkaline phosphatase, the observed rise in GGT was thought to be unrelated to cholestasis. According to the study protocol, hepatitis serology was assessed because of the increase in LFTs. Hepatitis A antigen was found positive (date of laboratory report: 23 Jul 2001) whereas HBsAg and anti-HCV were reported to be negative. The investigator judged these elevations to be a SAE possibly related to study drug. The patient was referred to his primary care physician and laboratory assessments were to be repeated until normalized.

Reviewer's comment: The reviewer believes that relationship of the LFT elevation to study drug can not be excluded.

Patient 47003: This patient has a history of hypertension (since March 2000 and is ongoing), hypercholesterolemia (since Mar 2000 and is ongoing), right ankle pain (since Jan 2000 and resolved on 05 Feb 2001), diabetes mellitus (since Jul 1998 and is ongoing), and esophagitis (since 1995 and is ongoing). Since commencing this trial he has had AEs of difficulty sleeping (ongoing), upper respiratory tract infection (resolved), cold sore-like spots (resolved), depression (ongoing), sleep deprivation (ongoing), elevated alkaline phosphatase (resolved), elevated GGT (resolved), elevated ALT (SGPT) (resolved), elevated AST (SGOT) (resolved), and elevated uric acid (resolved). The patient has been taking omeprazone magnesium (20 mg daily since 1995), flunitrazepan (4 mg daily since 25 May 2000 to 19 Jun 2000), indapamine hemihydrate (2.5 mg daily since 01 Aug 2000), eamitriptyline hydrochloride (100 mg daily since Sep 2000) and pergolide mesylate (250 mcg daily since Oct 2000). On 12 Sep 2000 the patient attended the clinic for his visit 5 appointment. A blood sample was collected at this visit which revealed the following clinically significant (coded by the investigator) abnormalities:
Elevated AST (SGOT) 127 U/L (normal range 11-36 U/L)
Elevated ALT (SGPT) 101 U/L (normal range 6-43 U/L)
Elevated GGT 125 U/L (normal range 10-61 U/L)
Elevated alkaline phosphatase 119 U/L (normal range 31-110 U/L)
Elevated uric acid 726 umol/L (normal range 196-446 umol/L)
The patient reported having a very large alcohol intake during the evening prior to attending this visit (approximately 12-18 hours prior to visit). The investigator considered that the elevated AST result was "unlikely" to be related to study medication. As a follow-up the patient had another blood sample collected on 10 Oct 2000. The following results were obtained:
AST (SGOT) 33 U/L (normal range 11-36 U/L)
ALT (SGPT) 38 U/L (normal range 6-43 U/L)

GGT 81 U/L (normal range 10-61 U/L)
Alkaline phosphatase 139 U/L (normal range 31-110 U/L)
Uric acid 411 umol/L (normal range 196-446 umol/L)
The investigator did not consider any of these laboratory results to be clinically significant.

Reviewer's comment: The elevated LFT's may have been related to alcohol ingestion.

Patient #6005: This patient had a history of right knee pain (since May 2000), benign hyperplasia of prostate (since 1991), arthritis (since 1995), cholelithiasis (since 1993) and erectile dysfunction diagnosed Nov 1993. There were no previous AEs reported from this patient. Concomitant Medication: The patient was given testosterone prior to inclusion in the study (250 mg, IM, from 27 Dec 1993 to Mar 1994) and diclofenac sodium for arthritis (100 mg, PO, from Jun 2000 to Jul 2000). During the study he was given ibuprofen for arthitic pain (400 mg, PO, since Jan 2001 and ongoing after end of study). CK was within normal values at screening (see table below). At visit 7 (dated 08 May 2001, last previous study drug intake dated 06 May 2001) CK value was over 500 U/L. CK-MB was attempted to be analysed but could not tested due to poor sample quality. At visit 8 (dated 04 Jul 2001, previous study drug intake dated 02 Jul 2001) CK value was increased (see table below) and CK-MB value was found above the upper normal range. ECG was completely normal and no symptoms were reported by the patient. The patient was contacted by phone on 10 Jul 2001 (8 days after last study drug intake), and was still asymptotic. The patient was followed-up by the investigator one month after last study drug intake. The ECG was still normal and CK had returned to normal (see table below). Patient explained that he was moving home in Apr 2001. During this period of time he was stressed due to family and economic problems and has had "physical stress" as well.

VISIT	DATE	LAST INTAKE	CK	CK-MB
Visit 1	29 Jun 2000	NK	[illegible] U/L	NK
Visit 2	18 Jul 2000	NK	[illegible] U/L	NK
Visit 3	29 Aug 2000	24 Aug 2000	NK	NK
Visit 4	21 Oct 2000	23 Oct 2000	[illegible] U/L	NK
Visit 5	02 Feb 2001	27 Jan 2001	[illegible] U/L	NK
Visit 6	08 May 2001	06 May 2001	[illegible] U/L	Bad quality of sample
Visit 7	04 Jul 2001	02 Jul 2001	[illegible] U/L	21.4 ng/ml
Visit 8 Retest	02 Aug 2001	02 Jul 2001	[illegible] U/L	NK

Patient 17/015: The patient's past medical history was unremarkable. On 15 Nov 2000 he complained of sinusitis and on 24 Nov 2000 of fever. In addition to the study drug the patient was taking a combination of myrtol/ limonen/ cineol (2 doses daily), ciprofloxacin (250 mg daily) and

paracetamol (2000 mg daily) because of the AE. In the period from 01 Dec 2000 to 14 Dec 2000 he was hospitalised for cholecystitis and hepatitis. The investigator concluded that the most likely reason for "intermittent hepatitis" was an undetermined infectious disease associated with fever >40 °C. The last dose of study medication was taken on 17 Nov 2000. A premature termination visit was performed and the laboratory results for visits 1, 2, 3, and 5 and for the premature termination visit were found to be "insignificant."

Trial 10152:

Patient #18-652 had a SGOT of 140 U/L and a SGPT of 105 U/L 2 days after last study drug intake.

Patient #02-137 who had a diagnosis of hepatic cirrhosis had an SGOT of 279 U/L and a SGPT of 176 U/L at Visit 3. At Visit 5, 44 days after the last intake of study drug, the values were normalized at 21 and 22 U/L.

Twenty-one patients in this open label trial experienced CK >3X ULN. Fourteen of these patients had CK values >ULN at baseline. The other 7 patients are described below:

Patient #10152-003-119 had a concomitant muscular contusion.

Patient #10152 –008-204 reported no adverse event; the increase of CK was observed only at Day 1 (748 U/L, CK-MB was normal). At Day 19, the value decreased to 258 U/L and was normalized thereafter. The patient was also taking Hyzaar® (Losartan + hydrocholorothiazide) for hypertension. He was lost to follow-up after Visit 3.

Patient #10152-006-311 withdrew from the study prematurely due to "hot flush." The abnormal CK value was noticed 46 days after the last drug intake.

Patient #10152-002-345 reported a value of 875 U/L at Visit 6 with normal CK-MB value, 39 days after the last study drug intake.

Patient #10152-001-410 reported an increase of CK (1880 U/L) at Day 1 (CK-MB was normal). At Day 28, the value was at 401 U/L and normalized at Day 91. He had no concomitant treatment.

Patient #10152-017-659 had a CPK of 732 U/L at Visit 3 with CK-MB value of 7.5 ng/mL in a context of cardiovascular risk factors (diabetes, hepatopathy, hypertriglyceridemia, and coronary insufficiency). An ECG was interpreted by the investigator as abnormal, but clinically not significant, without clinical symptoms. The patient discontinued the same day for personal reasons.

Patient #10152-005-720 had a CPK of 705 U/L at Visit 3 with normal CK-MB value. Two months later, CK decreased to 135 U/L and the ECG did not show any change with previous ECG. The patient completed the study course.

The two following patients presented with values over 10xULN:

Patient #10152-007-511 had a CPK of 313 at baseline which became elevated to 2552 U/L at Day 80 (Visit 5) with CPK-MB at 6.3 (ULN=5.0). The initial abnormal value was associated with high LDH (304; ULN:234), SGPT (70; ULN:43), SGOT (39; ULN:36) and hperuricemia (8.40; ULN:8.20) levels. The intensity was mild, no action was taken and a retest 3 days later showed a decrease to 522 U/L (CPK-MB=2.6). At Visit 6 (Day 175), CK value was at 236 U/L.

Patient #10152-004-524 had a CPK of 2339 U/L three days after the last study drug intake (Visit 6) without any CPK-MB determination. During treatment, the values varied from 184 U/L at baseline to 296 U/L for the highest value (Visit 5). No abnormal symptom was recorded on ECG, no adverse event was reported, no other abnormal values were seen on laboratory tests or urinalysis, and no concomitant treatment was taken during the study course. This value was assessed as not clinically significant by the investigator.

Reviewer's comment: The cause of the elevated CPK's in the above two cases in not clear to this reviewer. Neither patient experienced a clinical adverse event.

Clinical pharmacology studies:

Patient 010006-001-010 participating in 40 mg for14 days dose-tolerability study showed a progressive increase in liver parameters during treatment. Before the first drug administration, AST 9.6 u/l (normal range: 0-19 u/L), ALT 9.5 u/l (normal range: 0-23 u/L) and GLDH 0.8 u/l (normal range 0-4 u/L) were in the normal range. On treatment Day 7 an increase of these parameters was observed. After a further increase on treatment Day 8 up to AST 24.6 u/l, ALT 45.8 u/l and GLDH 5.5 u/l, administration of test substance was discontinued. On the following days liver parameters further increased up to AST 54.9, ALT 114.6 and GLDH 12.2 u/l on Day 10 (3 days after the last administration of study drug on Day 8), when the subject was hospitalized for "special diagnostic evaluation." Ultrasound of the liver was normal. Blood tests did not reveal evidence of viral hepatitis. The possibility that the liver function abnormalities were caused by a reaction to parabens, used as a preservative in the oral solution of BAY 38-9456, could not be ruled out. Twenty-four hours later the subject was discharged from the hospital and returned back to the study ward. Liver parameters then decreased from the maximum of AST 66 u/l and ALT 142 u/l on Day 12. On follow-up all parameters returned to the normal range.

Reviewer's comment: The elevated liver function tests in this patient may be secondary to study drug.

Notable creatine kinase (CK) changes occurred in one patient participating in the nitrate interaction Study 100305. Subject 1030 was a 42-year-old healthy, male who was entered into the study with elevated baseline CK levels. At screening, his CK was elevated at 543 U/L (normal range: 21 – 213.U/L). Six days later, just before randomization, a repeat CK level was found to be 296 U/L, which was still elevated but within the protocol allowable range of up to 3 times the upper limit of normal. During the first period (placebo), his CK levels remained high at 333 and 382 U/L. During the second period, his CK levels were 722 and 427 U/L, on Day 4 and 24 hours after a single dose of 10 mg vardenafil, respectively. Three days later a repeat laboratory evaluation revealed an elevated CK level of 2675 U/L with a CK-MB band of 21.4 ng/mL (absolute value, normal range: 0-5 ng/mL). The CK-MB band was less than 1% of the total CK level. When these results became available on the following day, additional laboratory evaluation at the revealed an elevated CK of 822 U/L (normal range: 75-170 U/L); the CK-MB band and a troponin level were within normal limits and there were no ECG changes to suggest myocardial ischemia. The subject's AST and ALT were elevated at approximately 10% over the ULN. Over the next 3 days, the CK levels fell to 698 U/L, a level close to this subject's screening CK level, troponin levels remained normal, and the AST and ALT returned to within normal limits. There was no clear history of strenuous exercise in this subject during these CK elevations. A consulting cardiologist's assessment indicated that the most likely explanation was some kind of myositis which could be either viral or autoimmune.

Reviewer's comment: This patients CK levels were elevated at baseline.

Trial 10047: In this pharmacokinetic study, 8 volunteers were given 40 mg vardenafil/day and 4 volunteers were given placebo. Four of the eight drug treated patients and three of four placebo patients experienced mild elevations of ALT. Three of the eight drug patients discontinued because of back pain.

Reviewer's comment: Mild elevations were seen in both the drug and placebo patients.

Trials 100249, 10128, 100250, 100285, 10125, 10152, and 100312 were reviewed for serious adverse events, discontinuations secondary to adverse events, and "clinically significant adverse events."

Those events related to LFT's and CK abnormalities are listed below.

Trial 100249:

LFT abnormality

Patient 022-034 (vardenafil 10 mg) (study drug discontinued) This 38-year-old man with a history of seasonal asthma took his final dose of study medication on 02 Aug 2000 (the date of the Visit 3 PK evaluation). He discontinued study medication due to elevated liver enzymes. Prior to this visit, the last dose taken by the patient was on 28 Jun 2000. At the time of discontinuation, CK was also elevated, presumably due to a recent weight-lifting program begun by the patient. No CK-MB fractionation was performed. The patient was instructed to temporarily stop his weight-lifting as well as the nutritional supplements he started along with his exercise program (chondroitin sulfate, glucosamine, and Proto-Whey). No other adverse events were reported. SGOT, SGPT and CK values are listed below.

	ALT (U/L)	AST (U/L)	CK (U/L)
Visit 1 (09 May 2000)	23	19	56
Visit 2 (09 June 2000)	40	26	229
Visit 3 (02 Aug 2000)	230	376	**29,940**
Visit 4 (07 Aug 2000)- term	111	33	977
Visit 4.1 (16 Aug 2000)- post	42	18	214
Visit 4.2 (23 Aug 2000)- post	41	23	Not done

Additionally, a hepatitis panel done on 02 Aug 2000 was negative for hepatitis A antibody, hepatitis B surface antigen and hepatitis C antigen. During the study, the patient also took a multivitamin, saw palmetto and vitamin E.

Reviewer's comment: The etiology of the increased LFT's is unclear. Study drug can not be excluded as a cause. In addition, study drug can not be excluded as a cause of the CPK elevation.

Patient 014-008: (vardenafil 10 mg) (study drug discontinued) This 51-year-old man with a history of HTN and deviated nasal septum repair discontinued study drug due to an adverse event of elevated liver enzymes, beginning at randomization (Visit 2), prior to the first dose of study drug. SGOT and SGPT values are shown below:

	SGOT (U/L)	SGPTU/L)
Visit 1 (19 Apr 2000)	28	48
Visit 2 (17 May 2000)	78	82
Visit 2.1 (08 Jun 2000)	124	132
Visit 3 (14 Jun 2000)- termination	78	127
Visit 3.1 (20 Jun 2000)- post study	65	119
Visit 3.2 (27 Jun 2000)- post study	31	61

The patient also reported adverse events of a common cold, intermittent lower bilateral back pain, intermittent right side pain and facial flushing. Concomitant medications included Neosynephrine (oxymetazoline) nasal spray, aspirin, Alka Seltzer (sodium bicarbonate/citric acid/aspirin), Tylenol (acetaminophen), generic Nyquil (pseudoephedrine/dextromethorphan/acetaminophen), and Tussin PE (guaifenesin).

Reviewer's comment: The patient's LFT's mildly elevated at baseline. An additional effect of study drug can not be totally excluded.

Patient 004-003 (vardenafil 10 mg) had an elevated ALT of 287 U/L prior to taking any study drug and study drug was discontinued.

Patient 044-053 (vardenafil 20 mg) This 72-year-old man with a history of HTN, prostate cancer with radioactive seed implants, diabetes, urinary urgency, constipation, hepatitis A and myopia had elevated ALT and AST on 26 Sep 2000 (Visit 6). Although study drug was dispensed at Visit 6, no more doses were taken, as study drug was discontinued after obtaining laboratory results. The patient's last dose of study drug was on 22 Sep 2000. The patient's ALT, AST, and alkaline phosphatase values are shown below.

	ALT (U/L)	AST (U/L)	Alkaline phos U/L)
Visit 1 (11 Apr 2000)	23	23	66
Visit 2 (11 May 2000)	24	21	67
Visit 3 (15 Jun 2000)	25	20	84
Visit 5 (15 Aug 2000)	29	28	62
Visit 6 (26 Sep 2000)	145	62	122
Visit 7 (02 Oct 2000)- term	50	26	79
Visit 7.1 (09 Oct 2000)- post	28	27	70
Visit 7.2 (16 Oct 2000)- post	32	25	65

Other adverse events reported by the patient were vomiting, diarrhea and flank pain. Concomitant medications included glyburide, atenolol, Detrol (tolterodine), PeptoBismol (bismuth subsalicylate), milk of magnesia, Mylanta (aluminum hydroxide/magnesium hydroxide/simethicone), glucosamine, and numerous vitamin and mineral supplements.

Trial 10128

LFT abnormality

Patient 040-748 (study drug discontinued) (sildenafil 50 mg). The patient, a 69-year-old, had a past medical history of hypertension from 1965, dyslipidemia from 1970, peptic ulcer 1986, right carotid endarterectomy 1986, left aorto-iliac prosthesis during 1988 and lower limb arteritis from 1986. He was on the following concomitant medication; amiloride, verapamil 240 mg and lisinopril 20 mg from 31 May 2000 for hypertension, atorvastatin 10 mg from 1998 for dyslipidaemia and clopidrogel 75 mg from 1999 for thrombosis prevention. The patient was started the run-in period on 09 Jun 2000. He experienced elevated liver function tests on 24 July 2000. On 28 July and again on 31 July, LFT's were repeated. The results are shown below:

	GGT	AST	ALT	alk phos
normal	35-131	10-50	11-36	6-35
26 Jun 2000	33	22	21	4
28 Jul 2000	505	173	289	151
31 Jul 2000	880	345	567	208

Serology for hepatitis was performed on 31 June and showed immunity against hepatitis A and B but no infection (HBsAG negative, HBs antibody positive 93.5ml units international per ml (positive more than 10), HBC antibody negative) and no immunity against hepatitis C (HBC antibody negative). The patient had a history of an episode of acute anemia and melena. The patient's history suggested upper GI bleeding and endoscopy revealed two ulcers. It was initially considered that the patient's elevated LFT's were related to lisinopril. Following discontinuation of lisinopril investigations were normal. On 14 August ALT was 43 (normal less than 40). Liver function tests and hepatitis C status were to be monitored. However at a later date (on 31 Aug 2000) the investigator changed the relationship between SAEs and study drug from none to probable.

Reviewer's comment: This patient was enrolled in the sildenafil group.

CK abnormality

Patient 040-396 (episode resolved) (sildenafil 50 mg) This 56-year-old man had a past medical history of hypertension. He was on lisinopril 2.5mg/day. The patient had an elevated CK level of 1251u/L (NR 18-198) on 20 Sep 2000. There was no history of excessive physical exercise or other symptoms to account for the raised CK. At baseline on 24 Aug 2000 the CK level had been normal (84u/L). A repeat CK on 23 Oct 2000 showed that the CK had returned to normal (71u/L). Following resolution of the elevated CK the patient took five further doses of study medication on 04, 08, 11, 15 and 18 Nov 2000 but the CK levels were not re-determined.

Patient 040-257 (episode resolved) This 49-year-old man had a past medical history of back pain (thoracic) 1970, infective hepatitis 1976, cholecystectomy 1988 and urticaria since 1998. He developed a frozen shoulder on 6 Sep 2000 but this condition resolved some time in Oct 2000. His concomitant medication included piriton for urticaria, codridomol for back pain, topical ibuprofen and vitamin supplements. On 16 October the patient was noted to have raised CK levels – 18690u/L.
Laboratory tests results are detailed below:

	26 Jun 2000	26 Jun 2000	16 Oct 2000	23Oct2000
CK (NR 18-198u/L)	74	84	18690	239
	16 Oct 2000			
CKMB (NR <5ng/ml)	7.5			
	16 Oct 2000	23 Oct 2000	30 Oct 2000	
ALT (NR 6-430u/L)	124u/L	59	25	
AST (NR 11-36u/L)	438u/L	36	22	
	16 Oct 2000	23 Oct 2000	30 Oct 2000	
Bi (NR 3-21 nmol/L)	34	39	35	

No ECG changes were noted on 21 Jun 2000, 19 Jul 2000, 14 Aug 2000, 16 Oct 2000 or 03 Nov 2000. Urinalysis on 16 Oct 2000 detected no abnormality. The patient gave no history of angina but said that he had acute muscle pain following an excessive work-out in the gym 2 days prior to the 16 Oct 2000. There was no evidence of myoglobinuria or viral infection. The patient was recalled on 23 Oct 2000 and his CK level was tested again with a reading of 239 u/L. The reading was within the normal range. The patient had finished taking the study medication on 15 Oct 2000.

Reviewer's comment: The patient participated in heavy physical activity, but the role of vardenafil in the increased LFT's and CK can not be excluded.

Trial 10125

LFT increases

Patient 13-026 (vardenafil 10 or 20 mg – blinded) The patient had a medical history of hypertension, hyperuricemia, BPH, colon polyps, and "hepatic steatosis." He received the following medications:
bisprololfumarate/hydrochlorothiazide (10 mg daily) and lisinoprile/ hydrochlorothiazide (10 mg per day) since 1996, alfuzosin (2.5 mg daily) since 07 Apr 2000 and allopurinol (150 mg daily) in the period from 24 May 2000 to 15 Jun 2000. He was evaluated at Visit 1 up to Visit 3 and Premature Termination Visit. The laboratory results of Visit 1 revealed elevated values of GGT (233 U/L), uric acid (507 µm/L), glucose (7.3 mmol/L), triglycerides (4.32 mmol/L). During Visit 2 to Visit V3 the value of GGT increased up to 314 U/L and that for triglycerides up to 17,10 mmol/L. The investigator felt that the elevation of the liver enzymes is likely to be due to alcohol consumption. As the patient was not willing to reduce his alcohol consumption,

the investigator decided to permanently withdraw him from study medication. The Premature Termination Visit was performed on 01 Sep 2000 and values of GGT (673 U/L), AST 44 U/L, AST (44 U/L), uric acid 517 µmol/L and glucose (12.3 mmol/L) were found increased again.

Reviewer's comment: The elevated LFT's are probably the result of alcohol consumption.

Patient 902-177 (vardenafil 10 or 20 mg – blinded) (episode resolved) The patient has a history of hypertension, intermittent heartburn, elevated GGT, penicillin allergy and mild insomnia. The patient drank 3 to 4 beers per day. Concomitant medications during the study period included Losartan Potassium for hypertension and flurazepam for mild insomnia. On 27 Jul 2000 about 1 month after starting study medication, the patient had an elevated bilirubin of 36 umol/L which the investigator felt was not clinically significant and unrelated to study medication. At the time the event was reported the value had dropped from nearly3x upper limit of normal to less than 2 x the upper limit of normal. There was no action taken and the patient reported no other adverse events. No cause for the elevated bilirubin was ever determined by the investigator. Lab values during the study period were as follows:

Analyte	Visit 1 (30 May 2000)	Visit 2 (29 Jun 2000)	Visit 3 (27 Jul 2000)	Visit 4 (28 Aug 2000)	Normal Range
Total Bilirubin	61 umol/L	39umol/L	36umol/L	19umol/L	3-21umol/L
GGT	141 U/L	103 U/L	93 U/L	88 U/L	10-61 U/L
ALT (SGPT)	27 U/L	22 U/L	22 U/L	18 U/L	6-43 U/L
AST (SGOT)	30 U/L	25 U/L	23 U/L	20 U/L	11-36 U/L
RBC	5.1 T/L	4.9 T/L	4.9 T/L	Not done	4.5-6.4 T/L

Reviewer's comment: This patient's bilirubin was elevated prior to receiving study drug.

CK elevation

Patient 15-023 (10 or 20 mg vardenafil – blinded) The patient was enrolled into the study (Visit 1) on 05 May 2000 and was randomized (Visit 2) on 07 Jun 2000. He had a medical history of Peyronie's disease (since 1990). Since 06 Nov 2000 concomitant medication included threonine (2 pills bid, dose unknown), zinc (oral, two pills bid, doses unknown) and magnesium (oral, 600 mg per day). From 22 May 1999 to Dec 1999 the patient used alprostadil (20 µg; intracorporal; on demand). The laboratory results from Visit 3 to Visit 5 revealed that the patient had elevated CK values, which increased on Visit 5 (05 Oct 2000) up to 1006 U/L (see table below). On Visit 6 (22 Dec 2000) the patient's CK value was nearly back to baseline (205 U/L). The investigator could not explain the elevated CK values, nor could the primary care physician or the internist.

The Investigator described the AE as not being related to study drug. The patient remained in the study.

	Visit 1 05 May 2000	Visit 2 07 Jun 2000	Visit 3 02 Aug 2000	Visit 4 25 Aug 2000	Visit 5 05 Oct 2000	Visit 6 22 Dec 2000	Visit 7 21 Apr 2000
CK (U/L)		171	342		1006	205	166

CLS reference range: CK: 18-198 U/L.

Reviewer's comment: The reason for the elevated CK is not clear.

Patient 18-004 (Vardenafil 10 or 20 mg – blinded) The patient had a medical history of BPH since 1998, shinbone and tibiofibular fracture in 1950, , herpes zoster infection (right face) in 1996 and cervical spine syndrome (since 06 Apr 2000) when he was enrolled in this study. He was randomized on 11 May 2000. In addition to the study drug, the patient was taking alfuzosin-HCl (5 mg per day). In the time from 13 Apr 2000 until 19 Aug 2000 he received diclofenac-Na (2 mg intramuscularly, per day) because of cervical spine syndrome The laboratory results from Visit 2 to 4 revealed that he had elevated values of CK, which increased on Visit 5 up to 1231 U/L (see table below). The investigator believed the elevation of the CK enzymes was likely due to the cervical spine syndrome and intramuscularly injections of diclofenac-Na, because on Visit 6 the patient's CK value was almost back to baseline. The patient remained in the study.

Table

	Visit 6	Visit 5	Visit 3	Visit 2
AST (U/L)	18	53	68	29
CK (U/L)	208	1231	764	396

Normal sub ranges: AST: 11-36 U/L, CK: 18-198 U/L

Reviewer's comment: The patient's elevated CK is plausibly related to the IM injections.

Patient 27-008 (vardenafil 10 or 20 mg – blinded) This patient did not have a significant past medical history. During the study the patient experienced knee trauma (adverse event) and took Nimesulida (200 mg daily, oral , 03 Aug 2000 - 08 Aug 2000). The patient had an elevated CK at 753 U/l at visit 3. The frozen sample for CK-MB value study was sent to ——— according to protocol, but the local laboratory mistakenly sent another patient sample. The sample in question was not analyzed. The CK had returned to normal by Visit 5. The investigator rated this event as "mild" and "possibly" related to study drug. No explanation for the elevated CK was determined. The patient had a CK of 281 U/l at the initial visit, before the beginning of study medication. The other laboratory results:

Visit 1 - CK 281 U/L
Visit 2 - CK 173 U/L
Visit 3 - CK 735 U/L

Visit 5 - CK 153 U/L (retest)
Visit 6 - CK 156 U/L
Visit 7 - CK 211 U/L
Visit 8 - CK 137 U/L

The patient has neither previous history of myocardial infarction or ECG abnormalities.

Reviewer's comment: The explanation for the elevated CK in this patient is not clear.

Patient 27-012 (vardenafil 10 or 20 mg – blinded) This patient did not have a significant past medical history. During the study he experienced had otitis media (adverse event), and took trimethoprim 160 mg + sulfamethoxazol 800 mg daily from 11 Mar 2001 to 13 Mar 2001 for this event. He experienced an elevated CK level on visit 3, visit 5 and visit 6, which normalized on visit 7. The investigator determined no reason for the elevated CK. He has no previous history of myocardial infarction. At Visit 5 an EKG showed first degree heart block which the investigator determined as not clinically significant.
TheCK results were:
Visit 1 - 181 U/L
Visit 2 - 173 U/L
Visit 3 - 243 U/L
Visit 5 - 232 U/L
Visit 6 - 262 U/L
Visit 7 - 139 U/L
Visit 8 - 123 U/L

Reviewer's comment: This event was mild and not clinically significant.

Summary: 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. In a few of the patients (#'s 105258, 10006-001010, and 022-034), no explanation for the elevated LFT's exists and causation by vardenafil can not be excluded. These elevations in transaminases are not associated with an elevated bilirubin. Increased transaminases may occur at a low incidence in the broad patient population and this information should be included in the label.

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

/s/

George Benson
7/22/02 02:06:34 PM
MEDICAL OFFICER

Mark S. Hirsch
7/23/02 12:21:27 PM
MEDICAL OFFICER
Please also see my memo.

Medical Officer's Review of NDA 21-400
Ophthalmology Consultation #2

Submission dates:	9/24/01, 2/17/03, 5/16/03
Review date:	7/22/03

Sponsor:	Bayer Corporation 400 Morgan Lane West Haven, CT 06516-4175 (203) 812-3051
Contact:	Gautam Shah, Ph.D.
Drug Product:	Levitra (vardenafil HCl tablets) 5, 10 and 20 mg
Pharmacologic Category:	PDE 5 Inhibitor
Proposed Indication:	Erectile dysfunction

Background:

Phosphodiesterase inhibitors have the potential to affect visual function. The mechanism is believed to involve the inhibition of PDE6, an enzyme found in the retina and thought to be responsible for phototransduction. The administration of Viagra (sildenafil tablets) has demonstrated dose dependent changes in visual perception and changes in Farnsworth-Munsell 100 hue testing and ERG testing.

Reviewed: Electronic Submission

Executive Summary

I. Recommendations

A. Recommendation on Approvability

From an ophthalmologic prospective, there is no objection to the approval of this NDA provided that the labeling is consistent with other phosphodiesterase inhibitors. Specific changes to the originally proposed labeling have been identified in this review.

There are many events listed in the Safety Update which deserve further follow-up. Specific problems are listed at the end of this review.

B. Recommendation on Phase 4 Studies and Risk Management Steps

It is recommended that repeated dose studies evaluating the effect of vardenafil on retinal function be conducted and submitted for review.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Three clinical studies evaluating vision were performed with vardenafil. Studies 100196 and 10197 demonstrate an effect of vardenafil on vision; however, the data set for study 100196 contains errors and cannot be trusted for accuracy. Study 100196 is also flawed by design and execution. The data set for study 10125 contains errors and cannot be trusted for accuracy.

B. Efficacy

Not evaluated in this review.

C. Safety

Minimal information is available from these studies; however, abnormal color vision was reported. No significant differences in safety in comparison to sildenafil can be determined.

Vision Studies

Title: Randomized, double-blind, placebo-controlled, 2-fold, cross-over study to investigate the influence of a single oral dose of 40 mg of BAY 38-9456 verum or placebo on retinal function in eye-normal healthy male subjects. (Protocol 10197)

Investigator: Peter Walter, MD.

Study Centre: Department of Ophthalmology
University Hospital Cologne
Joseph-Stelzamann-Str. 9
50931 Cologne, Germany

Dates of Study: 22 November 2000 through 30 March 2001.

Objectives

Investigate the possible influence of a single oral dose of 40 mg BAY 38-9456 on color vision in eye-normal male subjects, measured by the "Farnsworth-Munsell 100 test" at 1, 6 and 24 hours after dosing.

Study Design

Single center, double-blind, randomized, placebo-controlled, 2-way cross-over study performed on 25 healthy male subjects (17-57 years of age).

Reviewer's Comments: *25 patients may be enough to detect a change, but 25 patients are not enough to rule out an effect on vision.*

Schedule

Day	Screen	0d	0d	0d	0d	0d	0d	0d	0d	0d	0d	0d	1d	1-2
Hour	(-2 / -1	00	00	00	01	01	02	04	05	06	06	08	00	weeks
Minute	week)	-30	00	20	00	20	00	00	20	00	20	00	00	
Administration of BAY 38-9456*			X											
Lab: clinical chemistry/hematology	X											X		X
Urine for drug screening	X	X												
Eye-examinations:														
- Refraction (objective + subjective)	X			X					X				X	
- Vision – visual acuity (ETDRS)	X			X					X				X	
- Intraocular pressure	X			X					X				X	
- Slit-lamp	X			X					X				X	
- Humphrey 30-2 visual field test	X								X				X	
- Amsler test	X			X					X				X	
- Farnsworth-Munsell 100 test	X				X					X			X	
- ERG (incl. photo stress test)	X					X					X		X	
- Fundoscopy	X					X					X		X	
Well-being		X		X			X	X		X		X	X	X
Blood pressure, heart rate	X	X					X	X				X	X	X
ECG	X													X
Presentation at study ward		X												
Discharge												X		

* Two tables of 20mg of vardenafil (free base of BAY 38-9456): as tablet or corresponding placebo

Blood samples for population-pharmacokinetics (BAY 38-7268 and BAY 44-5576):

- at baseline (at screening; within 2 weeks before administration)
- between the following time intervals after administration of the test drug on the study days: 0-1h, 1-2h and 2-8h

- Subjective well-being and adverse events: asking of non-leading questions, in addition any change of the subjective well-being of the subjects was documented.
- Heart rate, blood pressure (systolic, diastolic, mean pressure): monitored in sitting position after a resting period of 15 minutes
- ECG-parameters (PR, QRSD, QT/QTc): a standard electrocardiogram (12-lead ECG) according to Goldberg/Einthoven and Wilson was recorded after a resting period of 15 minutes. The ECG was evaluated by an anesthesiologist of the University Hospital Cologne.
- Laboratory parameters -Hematology: leukocytes, erythrocytes, hemoglobin, hematocrit, platelets, reticulocytes, WBC, PTT, prothrombin time
- Clinical chemistry: AST, ALT, AP, GLDH, GGT, LDH, HBDH, CK, amylase, lipase, CHE, glucose, cholesterol (HDL, LDL, total), triglycerides, creatinine, urea, uric acid, bilirubin, total protein, sodium, potassium, calcium, chloride
- Drug screening and alcohol testing
- Opiates, amphetamines, cannabis, benzodiazepines, cocaine-metabolites; alcohol testing could be performed on suspicion of alcohol intake without prior announcement.
- Refraction (5 min): The best subjective refraction for far vision was examined using a manual phoropter.
- Vision - visual acuity (7 min): Visual acuity was tested after assessment of the best refractive correction for the far using Early Treatment Diabetic Retinopathy Study (ETDRS) charts in 4 m testing distance.
- Intraocular pressure (2 min): The intraocular pressure was tested using the Goldmann applanation tonometer.
- Slit-lamp (2 min): The anterior segment was evaluated using slit-lamp biomicroscopy.
- Humphrey 30-2 visual field test (20 min) (only done once on the study day): The visual field was tested using static perimetry. As a standard the Humphrey Field Analyzer was used with the program 30-2 and the Peridata software package.
- Amsler test (3 min): Standardized Amsler charts were used to identify disturbances or metamorphopsia in the central visual field.
- Farnsworth-Munsell 100 test 3 (30 min): For quantitative analysis of color vision the Farnsworth Munsell 100 Test was used.
- Administration of eye drops for mydriasis and waiting period (30 min): The waiting period in the dark was necessary to achieve dark adaptation as a prerequisite to perform electroretinography (ERG) according to international standards.
- ERG (including photo stress test) (35 min): The ERG consisted of rod driven responses, cone driven responses and a combination of both. The initial negative a-wave demonstrates the hyperpolarization of rods and cones after light stimulation whereas the positive b-wave indicates a depolarization of the postsynaptic retinal interneurons and the corresponding ionic currents along glial cells.
- Fundoscopy (5 min): The biomicroscopic evaluation of the fundus is done with the slit lamp and a 90 D fundus lens.

Inclusion criteria

- healthy, male, Caucasian, eye-normal subjects
- 18 to 65 years of age
- BMI between 20 and 32 kg/m^2
- no history of eye disease and/or surgery
- refraction: dioptry between +4 and –4
- normal findings after eye examination
- no clinically relevant ECG findings
- subjects who were able to understand and follow instructions and who are able to participate in the study for the entire period
- The eye-specific inclusion/exclusion criteria were examined for both eyes, however, only one eye was "randomized" for study use. The eye color was documented.
- Subjects must have given their written informed consent to participate in the study after receiving adequate previous information.

Exclusion criteria

The following factors determined at the pre-study examination automatically excluded the subject from participating in the trial:

- participation in another clinical trial during the preceding 3 months
- conspicuous findings in medical history and pre-study examination
- blood loss (e.g., blood donation) of >400 ml within the last 8 weeks prior to the start of the study
- history of relevant diseases of internal organs, of the central nervous system or other organs
- subjects with a medical disorder, condition or history of such that would impair the subject's ability to participate or complete this study in the opinion of the investigator or the sponsor
- Febrile illness within 1 week before the start of the study
- Subjects with a history of severe allergies, non-allergic drug reactions, or multiple drug allergies
- Subjects with a hypersensitivity to the investigational drug, the control agent and/or to inactive constituents
- regular daily consumption of more than one liter of beer or the equivalent quantity of alcohol in another form
- regular daily consumption of more than one liter of xanthine-containing beverages
- regular use of therapeutic or recreational drugs
- use of medication within the 2 weeks preceding the study which could interfere with the investigational product
- relevant deviation from the norm in the clinical examination
- relevant deviation from the norm in clinical chemistry or hematology
- resting heart rate in the awake subject below 45/min or above 90/min
- systolic blood pressure below 100 mmHg or above 160 mmHg
- diastolic blood pressure above 85 mmHg
- Relevant pathological changes in the ECG such as a first, second or third degree AV-block, prolongation of the QRS complex over 120 msec or of the QT_c-interval over 450 msec
- Positive testing in drug screening.

Disposition of subjects

A total of 25 subjects were enrolled in the study. Subjects 1 to 24 were randomly assigned to one of the two treatment sequences. Subject 16 was a member of the investigator's trial staff and for that reason excluded from further study participation by the sponsor after the first study period. He was replaced by Subject 116. Subject 116 was assigned to the same treatment sequence as Subject 16.

Protocol deviations

In some cases subjects could not perform the scheduled examinations exactly 24 hours after drug administration. The individual time deviations between the scheduled and actual investigation time for the primary outcome (Farnsworth-Munsell 100 test) 3 at "1d 0h 0m" are tabulated. One subject had a BMI of 19.7 kg/m^2 (inclusion criterion: 20-32 kg/m^2). These deviations were not considered relevant to the study outcome.

Demographic features		Subjects N = 25
Race	N (%) Caucasian	25 (100.0)
Gender	N (%) male	25 (100.0)
Color of eyes	N (%) brown	11 (44)
Age (years)	Median (range)	29.0 (18-57)
Height (cm)	mean (SD) [range]	179.6 (6.0) [168-191]
Weight (kg)	mean (SD) [range]	78.0 (9.2) [59-100]
Broca-Index (%)	mean (SD) [range]	98 (10)
BMI (kg/m²)	mean (SD) [range]	24.2 (2.5)

Farnsworth test *total error score* (mean ± SD)			
	40 mg BAY 38-9456 N = 24	BAY 38-9456 placebo N = 24	Difference active - placebo
Screening		58.4 ± 26.0	
1 h post drug administration	64.4 ± 34.4	49.9 ± 25.1	14.5 ± 27.0
6 h post drug administration	61.0 ± 33.7	51.1 ± 23.4	10.0 ± 26.5
24 h post drug administration	58.4 ± 31.0	57.6 ± 26.0	0.8 ± 19.0
Farnsworth test *error score line 1* (mean ± SD)			
Screening		11.2 ± 5.5	
1 h post drug administration	9.6 ± 8.5	9.8 ± 7.5	-0.2 ± 9.8
6 h post drug administration	10.3 ± 7.3	7.9 ± 6.8	2.5 ± 7.2
24 h post drug administration	11.2 ± 8.7	9.2 ± 5.0	2.0 ± 8.4
Farnsworth test *error score line 2* (mean ± SD)			
Screening		21.8 ± 14.2	
1 h post drug administration	20.1 ± 11.3	18.8 ± 7.4	1.4 ± 12.1
6 h post drug administration	22.0 ± 10.3	21.0 ± 9.7	0.9 ± 13.0
24 h post drug administration	25.6 ± 11.8	23.5 ± 10.1	2.1 ± 11.3
Farnsworth test *error score line 3* (mean ± SD)			
Screening		14.4 ± 8.4	
1 h post drug administration	20.2 ± 12.4	12.5 ± 11.0	7.7 ± 8.1
6 h post drug administration	15.9 ± 13.7	13.3 ± 11.1	2.6 ± 11.1
24 h post drug administration	11.7 ± 9.8	14.5 ± 13.4	-2.9 ± 11.1
Farnsworth test *error score line 4* (mean ± SD)			
1 h post drug administration	14.5 ± 11.3	8.8 ± 7.0	5.7 ± 9.0
6 h post drug administration	12.8 ± 11.8	8.9 ± 7.8	4.0 ± 12.1
24 h post drug administration	9.9 ± 9.2	10.5 ± 7.9	-0.5 ± 7.0

Reviewer's Comments: *Agree with sponsor that the most pronounced differences between the two groups were observed for the Farnsworth test total error score at 1 and 6 hours after drug administration and for the Farnsworth test error score line 3 and line 4 at 1 and 6 hours after drug administration (with 1 hour having demonstrating more pronounced effects than 6 hours).*

ERG – Mean ± SD

	40 mg N = 24	placebo N = 24	Difference active - placebo
ERG amplitude (μV), 2.4 cds/m²			
a-wave			
Screening		-128 ± 46	
1 h 20 min post administration	-102 ± 38	-114 ± 36	11.6 ± 45.2
6 h 20 min post administration	-104 ± 38	-116 ± 32	12.2 ± 41.1
24 h post administration	-103 ± 31	-116 ± 54	12.9 ± 46.2
b-wave			
Screening		225 ± 91	
1 h 20 min post administration	192 ± 50	202 ± 54	-9.9 ± 73.2
6 h 20 min post administration	224 ± 76	229 ± 58	-5.0 ± 90.2
24 h post administration	192 ± 42	230 ± 77	**-38.8 ± 71.0**
ERG latency (msec), 2.4 cds/m²			
a-wave			
Screening		22.3 ± 1.0	
1 h 20 min post administration	23.0 ± 1.6	22.6 ± 0.9	0.4 ± 1.4
6 h 20 min post administration	22.4 ± 1.0	22.6 ± 0.9	-0.2 ± 0.8
24 h post administration	22.6 ± 0.8	22.8 ± 1.1	-0.2 ± 0.8
b-wave			
Screening		43.1 ± 3.1	
1 h 20 min post administration	43.1 ± 4.1	43.8 ± 2.5	-0.7 ± 3.8
6 h 20 min post administration	44.0 ± 2.4	43.8 ± 2.2	0.2 ± 2.7
24 h post administration	43.8 ± 1.8	43.9 ± 2.7	-0.2 ± 2.2
ERG amplitude (μV), 5 cds/m²			
a-wave			
Screening		-33 ± 20	
1 h 20 min post administration	-31 ± 22	-35 ± 22	3.3 ± 29.8
6 h 20 min post administration	-31 ± 16	-26 ± 11	-5.0 ± 14.9
24 h post administration	-30 ± 12	-27 ± 19	-3.0 ± 17.3
b-wave			
Screening		92 ± 41	
1 h 20 min post administration	67 ± 27	83 ± 25	-15.4 ± 27.0
6 h 20 min post administration	81 ± 34	89 ± 31	-7.0 ± 42.9
24 h post administration	86 ± 24	96 ± 33	-10.9 ± 29.4
ERG latency (msec), 5 cds/m²			
a-wave			
Screening		14.4 ± 1.3	
1 h 20 min post administration	15.0 ± 2.1	14.5 ± 2.0	0.5 ± 2.2
6 h 20 min post administration	15.1 ± 2.2	14.4 ± 1.5	0.7 ± 2.2
24 h post administration	14.3 ± 2.1	14.3 ± 2.2	-0.0 ± 2.9
b-wave			
Screening		29.1 ± 1.7	
1 h 20 min post administration	29.5 ± 1.7	29.0 ± 1.4	0.5 ± 1.4
6 h 20 min post administration	28.8 ± 1.6	28.7 ± 1.1	0.0 ± 1.5
24 h post administration	28.9 ± 1.5	28.9 ± 1.8	-0.1 ± 1.2

ERG statistical results for b-wave

Parameter	Time	LS-mean active - placebo	95% Confidence limits lower	upper
Amplitude 2.4 cds/m^2	1 h 20 min post administration	-9.88 µV	-37.823	18.073
	6 h 20 min post administration	-4.96 µV	-32.906	22.99
	24 h post administration	**-38.79 µV**	**-66.740**	**-10.844**
Latency 2.4 cds/m^2	1 h 20 min post administration	-0.73 msec	-1.946	0.488
	6 h 20 min post administration	0.15 msec	-1.063	1.371
	24 h post administration	-0.15 msec	-1.367	1.067
Amplitude 5 cds/m^2	**1 h 20 min post administration**	**-15.38 µV**	**-27.867**	**-2.883**
	6 h 20 min post administration	-7.04 µV	-19.533	5.450
	24 h post administration	-10.92 µV	-23.408	1.575
Latency 5 cds/m^2	1 h 20 min post administration	0.52 msec	-0.102	1.144
	6 h 20 min post administration	0.02 msec	-0.607	0.640
	24 h post administration	-0.05 msec	-0.673	0.573

Reviewer Comments: *Electroretinogram b-wave amplitude was reduced.*

Visual Acuity - Log Mar for Study Eye

TREATMENT	TIME	N	MEAN	SD	MINIMUM	MEDIAN	MAXIMUM
NONE	SCREENING	24	-0.068	0.081		-0.070	
PLACEBO	0D 00H 20MIN	24	-0.079	0.075		-0.070	
	0D 05H 20MIN	24	-0.078	0.075		-0.060	
	1D 00H 00MIN	24	-0.097	0.079		-0.080	
VERUM	0D 00H 20MIN	24	-0.087	0.069		-0.080	
	0D 05H 20MIN	24	-0.061	0.059		-0.060	
	1D 00H 00MIN	24	-0.082	0.083		-0.100	

Reviewer Comments: *There was no difference in visual acuity, but the power to demonstrate a difference is small.*

Intraocular Pressure (mmHg) for Study Eye

TREATMENT	TIME	N	MEAN	SD	MINIMUM	MEDIAN	MAXIMUM
NONE	SCREENING	24	16.1	2.2		16.0	
PLACEBO	0D 00H 20MIN	24	14.8	1.8		15.0	
	0D 05H 20MIN	24	15.3	2.1		16.0	
	1D 00H 00MIN	24	15.1	2.1		16.0	
VERUM	0D 00H 20MIN	24	15.7	2.0		16.0	
	0D 05H 20MIN	24	16.1	2.1		16.0	
	1D 00H 00MIN	24	15.0	2.4		15.0	

Reviewer Comments: *There was no observed effect on intraocular pressure.*

Visual Field (Humphrey 30-2)

TREATMENT	TIME	N	GM(MD) MEAN	GM(MD) SD	GM(MD) MIN	GM(MD) MEDIAN	GM(MD) MAX	FS(FS) MEAN	FS(FS) SD	FS(FS) MIN	FS(FS) MEDIAN	FS(FS) MAX
NONE	SCREENING	24	1.29	1.76		1.50		120.80	18.28		121.90	
PLACEBO	0D 05H 20MIN	24	0.67	2.38		1.10		114.49	22.00		118.05	
	1D 00H 00MIN	24	1.59	1.45		1.10		123.41	17.00		118.25	
VERUM	0D 05H 20MIN	24	1.30	1.61		1.25		120.18	17.94		117.30	
	1D 00H 00MIN	24	1.26	1.45		1.05		120.05	15.69		117.20	

Reviewer Comments: *There was no difference in visual fields; the power to demonstrate a difference is small, and the table above is based on a single administration of drug product.*

Reviewer's Conclusions on Study 10197:

Study 10197 demonstrates an effect of vardenafil HCl on retinal function as measured by changes in color discrimination and ERG b wave amplitudes. There does not appear to be an effect on intraocular pressure. There is insufficient power in the study to evaluate the potential effect on visual acuity or visual field.

APPEARS THIS WAY
ON ORIGINAL