Title of the study: 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 [100196]

Investigator(s): Thomas L. Hunt, MD, PhD and Krishna Talluri, MD
Study center(s): Center 01 Austin, TX
Center 02 Morrisville, NC

Period of study: 16 February 1999 - 17 May 1999

Clinical phase: Phase 1

Objectives: The primary objective of this study was to determine the safety and tolerability of multiple-dose treatments of BAY 38-9456 in dosages up to 40 mg daily for 31 days in healthy middle-aged and elderly male subjects. The secondary objective was to define the multiple-dose pharmacokinetics of BAY 38-9456 and BAY 44-5576 (M-1, the expected main metabolite).

Methodology: This study was a randomized, double-blind, placebo-controlled, parallel-group trial of orally administered BAY 38-9456 in healthy middle-aged and elderly male subjects. Subjects were randomly assigned to 1 of 4 treatment groups: 20 mg BAY 38-9456 (QD) (12 subjects), 40 mg BAY 38-9456 QD (13 subjects), 40 mg BAY 38-9456 every other day (QOD) alternating with placebo (13 subjects), or placebo (12 subjects) QD. Subjects were screened within 3 weeks prior to receiving the first dose of study drug on Day 1. Screening included the following: complete medical history and physical examination, including height and weight; vital signs; color vision testing; PA and lateral chest X-ray; clinical laboratory tests including hematology, blood chemistry and urinalysis, hepatitis, and urine drug screens, and a serum TSH, T_3, and T_4 if a subject was receiving thyroid hormone replacement.

Reviewer's Comments: *Patients were required to be "In good health, as judged by both the investigator and sponsor, as evidenced by medical history, physical examination findings, clinical laboratory evaluation, electrocardiogram, chest x-ray and color vision testing." This was not always the case, as some patients (100196-001-1014, 1028, 1055; 100196-002-2046) had abnormal color vision at the screening visit. One patient had trauma (100196-001-1062, hit in left eye by tree branch) three days before the screening and is reported as recovering during the study. Patient 100196-001-1024 had a macular scar noted at screening.*

Subjects entered the clinic on the evening of Day –2. On the morning of Day –1, a 24-hour urine collection began for evaluation of liver enzyme induction. Subjects began fasting from 10 PM on the evening of Day –1 and continued to fast until 4 hours after dosing on Day 1. On the morning of Day 1, subjects received 20 mg BAY 38-9456 QD, 40 mg BAY 38- 9456 QD, 40 mg BAY 38-9456 QOD alternating with placebo, or matching placebo QD. Subjects were not allowed to drink for 2 hours before dosing, and they fasted for 4 hours after dosing.

A standard lunch was served 4 hours after dosing. On Day 1 and Day 31, plasma samples were collected for the determination of BAY 38-9456 and BAY 44-5576 predose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours after dosing. A plasma sample was collected at 30, 36, and 48 hours after dosing on Day 31. On Day 8 and Day 14, a trough plasma sample was collected predose. On Day 1 and Day 31, urine was collected in separate containers for possible future analysis of drug and metabolites at the following intervals: 0-4 hours, 4-8 hours, 8-12 hours, and 12-24 hours postdose. A predose urine "blank" was obtained on Day 1 only. A second 24-hour urine collection was done for evaluation of enzyme induction at steady state, beginning the morning of Day 30 and ending the morning of Day 31.
Subjects were monitored for safety and tolerability throughout the study by physical and ophthalmology examinations, vital signs, ECG, and clinical laboratory tests.
Approximately 7 and 30 days after the final dose on Day 31 (Day 38 and Day 61), the clinic staff contacted all subjects by telephone and conducted a Wellness Assessment.

Number of patients A total of 101 subjects were enrolled in the study and screened for eligibility; 50 subjects were randomly assigned to one of the 4 treatment groups. The 50 subjects were randomly assigned to study drug treatment as follows: placebo (12 subjects); 20 mg BAY 38-9456 QD (12 subjects); 40 mg BAY 38-9456 QOD (13 subjects); and 40 mg BAY 38-9456 QD (13 subjects). Forty-seven subjects completed the 31-day treatment period.
Subjects ranged in age from 45 to 70 years, and in weight from 58.7 to 128.5 kg. The ethnic composition of the study population was 41 Caucasian, 6 Black, 1 American Indian, and 2 Hispanic.

Reason for Screen Failures	Number of Subjects
Protocol violation	32
Consent withdrawn	5
Sponsor/investigator exclusion	11
Lost to follow-up	2
Atrial bigeminy	1
Total	51

Source: Listing Section 16.2.10, Data Listing 21.

Selected Demographic and Baseline Characteristics				
		BAY 38-9456	BAY 38-9456	BAY 39-9456
	Placebo	20 mg QD	40 mg QOD	40 mg QD
Variable	(N=12)	(N=12)	(N=13)	(N=13)
Race, N (%)				
Caucasian	12 (100)	11 (92)	12 (92)	6 (46)
Black		1 (8)	1 (8)	4 (31)
American Indian				1 (8)
Hispanic				2 (15)
Mean age [years] (±std dev)	55.3 (6.7)	53.3 (8.2)	52.4 (6.3)	53.7 (8.1)
Range	47-70	45-66	45-64	45-68
Mean Weight [kg] (±std dev)	89.7 (15.5)	86.1 (12.1)	84.5 (10.1)	82.6 (9.0)
Range	70.8-128.5	69.0-107.7	68.4-100.8	58.7-93.1
Mean height [cm] (±std dev)	180.7 (8.0)	179.4 (7.1)	179.9 (5.9)	179.2 (7.5)
Range	164.1-193.0	167.6-191.0	170.2-190.5	161.0-188.0
Source: Section 14.1, Table 1				

During the 31-day treatment period, subjects took 20 mg BAY 38-9456, 40 mg BAY 38-9456, or placebo once daily. Study drug was administered in the morning between 7:00 AM and 10:00 AM. Immediately after ingesting study drug, subjects drank 180 mL of tap water. The dose was administered as 1 or 2 x 21.5 mL BAY 38-9456 0.1% oral solution or matching placebo solution. Study drug was packaged in bottles and each bottle contained 20 mg BAY 38-9456 base or matching placebo

Reviewer's Comments: *Unfortunately there are errors in the database for the ophthalmic examinations. Final conclusions should not be drawn from this study until the database is corrected. For example: Patient 100196-001-1007 is listed as having a spherical refraction of 67 diopters in each eye. It is highly unlikely that this is physiologically possible.*

Ophthalmic Testing:

Ophthalmic Testing included:

- Ocular symptoms
- Best corrected distance visual acuity
- Color vision (Ishihara)
- Visual fields (Amsler grid method)
- Gross External Examination
- Pupillary reaction
- Motility
- Slit Lamp Examination of anterior segment
- Intraocular Pressure (applanation)
- Dilated Ophthalmoscopy

Reviewer's Comments:

The use of an Ishihara examination for color vision is inappropriate because this test does not detect common acquired defects in the blue-yellow discrimination area.

The use of Amsler grid for visual fields is not appropriate because this test is not sufficiently sensitive to detect many changes in the visual field.

The study report states that there were no clinically significant changes detected on ophthalmic examination. There are no summaries of the ophthalmic information and it does not appear that any attempt was made to coordinate or review this information. However, there were numerous clinical findings reported in the examinations. Some of them are listed below.

Patient 100196-001-1008 had an elevation of IOP from 16 to 24 mmHg.
Patient 100196-001-1013 had ocular redness, puntate staining of the cornea and changes in the lens.
Patient 100196-001-1004 reported dimmer vision.
Patien: 100196-001-1007 reported halo distortion.
Patient 100196-002-2045 reported red vision.
Patient 100196-002-2055 reported blue vision.
Patient 100196-002-2056 reported a blue tint in the background.

Two of 8 subjects who experienced visual changes on 40 mg BAY 38-9456 had blue color vision changes by ophthalmic exam near the time of C_{max}.

Pharmacokinetic Parameters for BAY 39-9456 on Days 1 and 31

Parameter[a]	20 mg QD (n=12)[b]		40 mg QOD (n=13)		40 mg QD (n=13)	
Day 1						
AUC_{0-24} (µg*h/L)	70.1	(39%)	130.3	(47%)	136.6	(52%)
$AUC_{0-\infty}$ (µg*h/L)	71.5	(40%)	132.5	(48%)	138.7	(53%)
C_{max} (µg/L)	17.0	(41%)	29.5	(48%)	30.9	(53%)
T_{max} (h)	0.9	(36%)	0.9	(44%)	1.3	(48%)
t½ (h)	4.2	(37%)	4.2	(39%)	4.2	(30%)
Day 31						
AUC_{0-24} (µg*h/L)	75.7	(47%)	127.2	(56%)	139.0	(52%)
C_{max} (µg/L)	16.6	(47%)	30.2	(45%)	31.0	(50%)
T_{max} (h)	0.9	(41%)	1.0	(47%)	1.1	(32%)
t½ (h)	5.1	(34%)	4.6	(32%)	4.8	(41%)
AR[c], AUC (%)	111.4	(30%)	97.6	(25%)	100.3	(22%)
AR, C_{max} (%)	99.4	(31%)	102.4	(38%)	98.8	(30%)

[a]Presented as geometric mean (coefficient of variation)
[b]n=11 for Day 31
[c]AR = accumulation ratio

Treatment-Emergent Adverse Events Reported by at least 2 Subjects in a Treatment Group

		BAY 38-9456		
COSTART Term	Placebo (n=12)	20 mg QD (n=12)	40 mg QOD (n=13)	40 mg QD (n=13)
Any Event	6 (50%)	10 (83%)	12 (92%)	12 (92%)
Headache	1 (8%)	6 (50%)	6 (46%)	7 (54%)
Back pain	0 (0%)	3 (25%)	3 (23%)	7 (54%)
Asthenia	1 (8%)	3 (25%)	2 (15%)	1 (8%)
Pain	1 (8%)	2 (17%)	2 (15%)	2 (15%)
Leg pain	1 (8%)	3 (25%)	2 (15%)	1 (8%)
Neck rigidity	0 (0%)	0 (0%)	0 (0%)	2 (15%)
Accidental injury	2 (17%)	0 (0%)	0 (0%)	0 (0%)
Vasodilatation	1 (8%)	1 (8%)	2 (15%)	0 (0%)
Dyspepsia	2 (17%)	4 (33%)	3 (23%)	5 (38%)
Diarrhea	1 (8%)	1 (8%)	2 (15%)	4 (31%)
Myalgia	0 (0%)	1 (8%)	2 (15%)	2 (15%)
Dizziness	0 (0%)	2 (17%)	3 (23%)	2 (15%)
Somnolence	2 (17%)	0 (0%)	0 (0%)	0 (0%)
Rhinitis	2 (17%)	1 (8%)	1 (8%)	2 (15%)
Rash	0 (0%)	0 (0%)	2 (15%)	0 (0%)
Pruritus	0 (0%)	0 (0%)	2 (15%)	0 (0%)
Abnormal vision	0 (0%)	0 (0%)	3 (23%)	4 (31%)
Photophobia	0 (0%)	0 (0%)	2 (15%)	1 (8%)
Amblyopia	1 (8%)	0 (0%)	2 (15%)	0 (0%)
Conjunctivitis	2 (17%)	1 (8%)	0 (0%)	1 (8%)
Erections increased	0 (0%)	0 (0%)	2 (15%)	4 (31%)
Priapism	0 (0%)	0 (0%)	2 (15%)	0 (0%)
Urinary frequency	0 (0%)	0 (0%)	2 (15%)	0 (0%)

Source: Section 14.3.1, Table 1

Sponsor's Conclusions:
There was no apparent relationship between BAY 38-9456 dose group and individual events except for back pain, diarrhea, and abnormal vision. Three subjects in the BAY 38-9456 20 mg QD group (25%) and the 40 mg QOD group (23%) reported back pain compared with 7 (54%) subjects in the 40 mg QD group. One (8%) subject in the BAY 38-9456 20 mg QD group and 2 (15%) subjects in the 40 mg QOD group reported diarrhea compared with 4 (31%) subjects in the 40 mg QD group. None (0%) of the subjects in the BAY 38-9456 20 mg QD group reported abnormal vision compared with 3 (23%) subjects in the 40 mg QOD group and 4 (31%) subjects in the 40 mg QD group. The color vision abnormalities were confirmed in only 2 of these subjects on interim ophthalmic examination.

Reviewer's Conclusions concerning study 100196

This study is of little value because:

1. *It included patients in violation of the inclusion criteria which were important in assessing changes in vision.*
2. *It used tests which were insufficiently sensitive to detect changes in color vision and visual field.*
3. *It failed to identify observed changes from baseline.*
4. *It included only a small number of patients.*
5. *The numerical values did not appear to be correctly entered in the database, so it is not possible to determine which entered values are correct.*

Treatment Emergent Adverse Events Related to the Eye or Vision (Pool 3)

Visual Event	Placebo (N = 793)	Vardenafil (N = 1812)
Conjunctivitis	2 (0.3%)	16 (0.9%)
Abnormal vision	2 (0.3%)	11 (0.6%)
Amblyopia	1 (0.1%)	7 (0.4%)
Photophobia	0 (0.0%)	7 (0.4%)
Eye hemorrhage	0 (0.0%)	5 (0.3%)
Lacrimation disorder	0 (0.0%)	5 (0.3%)
Cataract specified	0 (0.0%)	4 (0.2%)
Eye pain	0 (0.0%)	3 (0.2%)
Dry eyes	0 (0.0%)	2 (0.1%)
Glaucoma	0 (0.0%)	2 (0.1%)
Chromatopsia	0 (0.0%)	1 (<0.1%)
Corneal lesion	0 (0.0%)	1 (<0.1%)
Eye disorder	0 (0.0%)	1 (<0.1%)
Mydriasis	0 (0.0%)	1 (<0.1%)
Refraction disorder	0 (0.0%)	1 (<0.1%)
Retinal disorder	0 (0.0%)	1 (<0.1%)
Retinal hemorrhage	0 (0.0%)	1 (<0.1%)
Blindness	1 (0.1%)	0 (0.0%)
Vitreous disorder	1 (0.1%)	0 (0.0%)

Pool 3, Table 2/1.1

There were 3 special senses adverse events that led to premature discontinuation in the vardenafil group compared to none in the placebo group. These events were abnormal vision (1), conjunctivitis (1), and lacrimation disorder (1). There were no serious adverse events related to eye symptoms or vision in either placebo or vardenafil treatment groups.

Sponsor's summary

In summary, vardenafil treatment was associated with a low incidence of adverse events related to vision and eye complaints and most of these were of mild intensity. Most patients who experienced these side effects continued on treatment, and serious visual adverse events related to treatment were not observed. In Clinical Pharmacology studies doses higher than those tested in the Phase III clinical trials resulted in changes of color vision in the blue/green hue range. These changes were most pronounced by 1 hour, improved by 6 hours, and had resolved by 24 hours after dosing. The transient change in color vision is associated with a mild reduction of the cone driven b-wave amplitude. However, color vision change was reported rarely (<0.1%) with vardenafil treatment in the clinical studies.

Title of the study: A randomized, double-blind, multi-center, fixed-dose, parallel group twelve month study to investigate the safety and tolerability of the phosphodiesterase type 5 inhibitor vardenafil in the treatment of patients with erectile dysfunction. [10125]

Investigator(s): The principal investigator was Dr. Inigo Saenz de Tejada
Fundacion para la investigacion y el desarrollo en andrologia sc/Antonio Robles 4, 9o C 28034 Madrid, Spain

Study centers: The study was conducted at 72 centers in Argentina, Australia, Brazil, Canada, Chile, Germany, Israel, Mexico, South Africa, Spain, and the United States

Period of study: 06 Apr 2000 to 27 Aug 2001 (First patient's first visit to last patient's last visit)

Clinical phase: Phase III

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

Methodology: This was a multicenter, randomized, double-blind, fixed dose, 2-arm, parallel group comparison study of 10 mg and 20 mg of vardenafil in men with ED. The overall design consisted of a 4-week baseline (no treatment, including devices) period, a 52-week double-blind treatment period, and a follow-up period of 7 days to collect data concerning serious adverse events (SAEs).

Number of patients: 1020 male patients were enrolled in this study at 72 centers (median age 57 years, age range 18-89 years). The median treatment duration was 345 days. The total number of premature terminations was 265 (151 with vardenafil 10 mg and 114 with 20 mg).

Diagnosis and main criteria for inclusion:
Patients in the study were men ≥18 years of age in relatively good health who had ED for more than 6 months.

Test product, dose and mode of administration, batch number:
Vardenafil 10 mg tablet, oral administration about 1 hour before intended sexual intercourse, no more than 1 dose to be taken within a calendar day

Vardenafil 20 mg tablet, oral administration about 1 hour before intended sexual intercourse, no more than 1 dose to be taken within a calendar day.

Criteria of evaluation:
Efficacy: Efficacy in general was a secondary criterion in this study. The main parameters were pertinent diary questions (Sexual Encounter Profile), particularly concerning the ability to penetrate and maintain erection during intercourse, as well as the erectile function (EF) domain score of the International Index of Erectile Function (IIEF) and the global assessment question (GAQ). Other efficacy variables included scores from the Fugl-Meyer Life Satisfaction Checklist and the Center for Epidemiologic Studies Depression Scale (CES-D).

Safety: The primary goal of the study was to compare the safety and tolerability of two doses of

vardenafil. Safety and tolerability were assessed on grounds of laboratory evaluation (hematology, blood chemistry, urinalysis); physical examination; eye examination (in North American patients only); measurements of blood pressure, heart rate, and body weight; adverse events (AEs) data; and electrocardiogram (ECG).

Sponsor's Summary of Ophthalmic Safety

There was no evidence for relevant differences between the two treatment groups in terms of vital signs, ECG assessments or findings from eye examinations and ophthalmology interviews (eye examinations performed in North American patients only).

Ocular Motor Balance

Group	Week	Right Eye				Left Eye			
		Baseline Normal		Baseline Abnormal		Baseline Normal		Baseline Abnormal	
		Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal
10	13	76	0	0	4	74	2	0	3
10	52	65	1	3	1	63	3	2	1
20	13	82	0	2	0	81	2	2	1
20	52	65	0	1	1	65	0	1	1

Reviewer's Comments: *Minimal changes observed. Limited number of patients evaluated.*

Conjunctiva

Group	Week	Right Eye				Left Eye			
		Baseline Normal		Baseline Abnormal		Baseline Normal		Baseline Abnormal	
		Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal
10	13	70	1	4	5	70	1	2	5
10	52	63	2	3	2	63	2	1	2
20	13	76	2	3	5	78	2	2	4
20	52	59	3	2	3	59	3	1	4

Reviewer's Comments: *Abnormal findings from 1-5%. Limited number of patients evaluated.*

Slit Lamp Exam

Group	Week	Right Eye				Left Eye			
		Baseline Normal		Baseline Abnormal		Baseline Normal		Baseline Abnormal	
		Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal
10	13	76	2	3	6	70	2	1	6
10	52	60	5	3	3	59	6	2	1
20	13	85	0	0	8	79	1	2	5
20	52	65	1	0	5	59	3	4	1

Reviewer's Comments: *Abnormal findings from 1-11%. Limited number of patients evaluated.*

Anterior Chamber Depth

Group	Week	Right Eye		Left Eye	
		Baseline Normal	Baseline Abnormal	Baseline Normal	Baseline Abnormal

		Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal
10	13	78	1	1	1	77	2	1	1
10	52	69	0	1	0	69	0	1	0
20	13	84	0	1	1	85	0	0	1
20	52	64	1	1	1	66	1	0	1

Reviewer's Comments: *Minimal changes observed. Limited number of patients evaluated.*

Lens

Group	Week	Right Eye				Left Eye			
		Baseline Normal		Baseline Abnormal		Baseline Normal		Baseline Abnormal	
		Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal
10	13	44	3	1	33	45	3	1	32
10	52	35	5	3	27	36	5	2	27
20	13	48	7	4	26	48	7	5	24
20	52	32	8	2	25	30	11	2	23

Reviewer's Comments: *Abnormal findings were reported in between 6 and 25%.*

Fundus

Group	Week	Right Eye				Left Eye			
		Baseline Normal		Baseline Abnormal		Baseline Normal		Baseline Abnormal	
		Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal
10	13	64	4	2	10	62	4	2	12
10	52	48	6	5	10	46	4	4	15
20	13	73	2	1	10	73	3	0	8
20	52	56	3	0	8	51	8	0	6

Reviewer's Comments: *Abnormal findings were reported in between 4 and 12%.*

Amsler Grid

Group	Week	Right Eye				Left Eye			
		Baseline Normal		Baseline Abnormal		Baseline Normal		Baseline Abnormal	
		Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal
10	13	58	2	2	0	58	1	2	1
10	52	52	1	2	0	51	1	2	1
20	13	69	2	0	1	65	2	2	2
20	52	53	2	0	0	49	4	1	0

Reviewer's Comments: *Minimal changes observed. Limited number of patients evaluated.*

ERG

Group	Week	Right Eye				Left Eye			
		Baseline Normal		Baseline Abnormal		Baseline Normal		Baseline Abnormal	
		Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal
10	13	26	4	3	2	27	2	3	3
10	52	17	3	1	0	18	2	1	0
20	13	31	4	0	2	30	3	1	3
20	52	15	5	1	0	16	3	2	0

Reviewer's Comments: *Abnormal findings were reported in between 12 and 25%.*

Visual Acuity

Group	Week	Right Eye					Left Eye				
		N	N Missing	Mean	Min	Max	N	N Missing	Mean	Min	Max
10	Baseline	90	0	29.9			92	58	27.1		
10	13	81	0	25.0			80	69	25.1		
10	52	70	0	36.6			70	46	40.8		
20	Baseline	89	0	28.3			93	66	36.4		
20	13	85	1	28.5			86	73	28.5		
20	52	67	0	30.1			68	57	39.1		

Reviewer's Comments: *The reported values in this table are flawed.*

1. *Reported visual acuity values of 0, 151, 153, 201 and 203 are not consistent with the equipment used to measure visual acuity.*
2. *The N (number of patients evaluated) cannot be approximately the same in the right and left eye since the "N Missing" values vary between eyes by over 50 observations.*

Since the numbers reported in the table are not believable, conclusions from the data are also not believable.

IOP

Group	Week	Right Eye					Left Eye				
		N	N Missing	Mean	Min	Max	N	N Missing	Mean	Min	Max
10	Baseline	89	1	15.0			89	1	15.1		
10	13	80	1	15.4			80	1	15.5		
10	52	70	0	14.9			70	0	15.1		
20	Baseline	87	2	15.6			87	2	15.6		
20	13	84	2	15.6			84	2	15.4		
20	52	66	1	15..7			66	1	15.4		

Reviewer's Comments: *No significant abnormalities above baseline;, however, several patients had elevated intraocular pressure at baseline.*

FM100

Group	Week	Right Eye					Left Eye				
		N	N Missing	Mean	Min	Max	N	N Missing	Mean	Min	Max
10	Baseline	74	16	123.9			74	16	120.0		
10	13	78	3	108.1			77	4	110.0		
10	52	55	15	104.1			54	16	109.6		
20	Baseline	76	13	103.1			74	15	106.0		
20	13	83	3	105.3			82	4	106.3		
20	52	60	7	94.8			60	7	100.2		

Reviewer's Comments:

1. *It is not clear what scoring system was used since the traditional scoring system for the FM100 includes only even integers.*
2. *The 20 mg group appears to demonstrate decreased color vision. Normal testing would have been expected to demonstrate improvement in the scores because of the learning curve routinely observed with the Farnsworth-Munsell 100 Hue test.*

Table 14.3.1/1 16NOV2001
Male erectile dysfunction incidence rates of adverse events
By body system and treatment
Population: patients valid for safety

	10mg		20mg	
ADVERSE EVENT	(N=514)		(N=506)	
SPECIAL SENSES				
Any Event	64	(12%)	61	(12%)
Abnormal Vision	8	(2%)	13	(3%)
Amblyopia	6	(1%)	6	(1%)
Blepharitis	1	(<1%)	0	(0%)
Cataract Specified	4	(1%)	5	(1%)
Chromatopsia	2	(<1%)	4	(1%)
Conjunctivitis	13	(3%)	7	(1%)
Corneal Lesion	0	(0%)	1	(<1%)
Deafness	1	(<1%)	0	(0%)
Diplopia	1	(<1%)	1	(<1%)
Dry Eyes	0	(0%)	1	(<1%)
Ear Disorder	1	(<1%)	0	(0%)
Ear Pain	3	(1%)	1	(<1%)
Eye Disorder	9	(2%)	6	(1%)
Eye Hemorrhage	1	(<1%)	1	(<1%)
Eye Pain	2	(<1%)	2	(<1%)
Glaucoma	2	(<1%)	1	(<1%)
Lacrimation Disorder	0	(0%)	4	(1%)
Otitis Externa	3	(1%)	1	(<1%)
Otitis Media	6	(1%)	4	(1%)
Photophobia	1	(<1%)	5	(1%)
Pigment Deposits Lens	1	(<1%)	1	(<1%)
Retinal Disorder	3	(1%)	2	(<1%)
Retinal Hemorrhage	1	(<1%)	0	(0%)
Retinal Pigmentation	1	(<1%)	0	(0%)
Special Senses Surgery	8	(2%)	3	(1%)
Strabismus	1	(<1%)	0	(0%)
Tinnitus	1	(<1%)	4	(1%)
Vitreous Disorder	0	(0%)	1	(<1%)

Notes: incidence rate = # of patients reporting an event / # of patients valid for safety

Safety Update:

The NDA Major Amendment 3-Month Safety Update Pool 4 has no new serious adverse events related to visual safety, and the overall rates of treatment-emergent abnormal visual findings remained consistent with the NDA Major Amendment Pool 4. However, in Study 10786, there were new treatment-emergent adverse events related to vision: 2 patients with conjunctivitis, 1 patient with abnormal vision, 4 patients with amblyopia, 1 patient with an eye disorder, 2 patients with glaucoma, and 1 patient with a retinal disorder. The new vision-related adverse events were assessed as drug-related according to the investigator in 1 case of conjunctivitis, 1 case of abnormal vision, 3 cases of amblyopia, 1 case of eye disorder, and 2 cases of glaucoma. Study medication was discontinued in one patient with abnormal vision (Patient 10786-041-004). This patient, a 62-year old man, noted a change in vision one hour after taking vardenafil 10 mg. The symptoms resolved within an hour. There were no serious adverse events related to vision in ongoing studies between 15 Oct 2002 and 15 Jan 2003.

Reviewer's Comments: *Some of these cases will be discussed in more detail below. It should be noted that the term "amblyopia" is being used incorrectly. Amblyopia specifically refers to a reduction in visual acuity not attributable to a structural abnormality of the eye or posterior visual pathway. It is not synonymous with "blurred vision."*

Specific Adverse Events Reported in Safety Update:

Patient identifier 010573-120-0002 **Date of birth** 1940
Sex M **Height (cm)** 173 **Baseline weight (kg)** 55
Race Caucasian **Study drug** BAY 38-9456 10 mg
Start/stop dates of study drug 17 May 2000 (Study 010125) until 10 Jun 2002
Event 1. Mild infection both eyes (Investigator term) Conjunctivitis (COSTART term)
2. Nystagmus both eyes (Investigator term) Nystagmus (COSTART term)

Severity	1. and 2. Mild
Serious (yes/no)	1. and 2. No
Start/stop date of event	1. and 2. 15 Nov 2001 to ongoing
Date of last dose of study drug before event	1. and 2. 15 Nov 2001
Action taken	1. and 2. None
Outcome of event	1. and 2. Unchanged
Relationship to study drug	1. and 2. Possible

Narrative:
This patient who was 59 years old when he received study medication for the first time had a history of bilateral arthritis of both shoulders ongoing since 1995. Concomitant medication included St John's Wort 1 tablet daily, saw palmetto 1 tablet daily and gingko bilboba 1 tablet daily for well being. Other medication during follow up phase - none. This patient had developed a mild infection of both eyes and nystagmus on Day 548 of treatment ongoing unchanged until end of this follow up study. No action was taken. A possible relationship to study medication was assessed by the investigator.
The patient completed the study.

Reviewer's Comments: *Nystagmus should be considered a serious adverse event. The patient should continue to be followed.*

Patient identifier 010573-101-0374 **Date of birth** 1946
Sex M **Height (cm)** 173 **Baseline weight (kg)** 77
Race Caucasian **Study drug** BAY 38-9456 10 mg
Start/stop dates of study drug 15 Aug 2000 (Study 010125) until 24 Jul 2002
Event Macular hole of left eye (Investigator term) Retinal disorder (COSTART term)
Severity Mild
Serious (yes/no) No
Start/stop date of event 28 Feb 2002 until 25 Jul 2002
Date of last dose of study drug before event 26 Feb 2002
Action taken Other
Outcome of event Resolved
Relationship to study drug Unlikely
Narrative:
This patient who was 43 years old when study medication was administered for the first time had a history of hay fever since 1950, food allergy since 1991, hypothyroidism since 1997 and carpal tunnel syndrome of right hand since 10 Jun 2001. For his allergic conditions he received Allergy Shots prn, Claritin (loratadine) prn and for hypothyroidism Levoxyl (levothyroxine) 50 mcg qd. On day 563 of treatment (28 Feb 2002) a macular hole of left eye was reported as medical important event. The patient was transferred to an eye specialist for a consultation. No treatment was administered and the event resolved without any further action taken. Before this event, the patient had cold symptoms and bronchitis, both conditions resolved before onset of the eye symptoms. During the ongoing event he had intermittent headaches (from 22 Apr 2002 until 15 Jun 2002) of mild intensity that resolved at end of study as well as pain of the right shoulder of mild intensity, ongoing until end of observation period. The patient completed the study.

Reviewer's Comments: *The reporting of this event is questionable. Macular holes are highly unlikely to resolve without any further action.*

Patient identifier 010573-120-0035 **Date of birth** 1934
Sex M **Height (cm)** 177 **Baseline weight (kg)** 85
Race Hispanic **Study drug** BAY 38-9456 10 mg
Start/stop dates of study drug 10 Jun 2000 (Study 010125) until 14 Jun2002
Event 1. Visual blue tint spots (Investigator term) Chromatopsia (COSTART term)
2. Pinguecula both eyes (Investigator term) Conjunctivitis (COSTART term)
3. Laceration right eye (Investigator term) Accidental injury (COSTART term)
4. Eye infection right (Investigator term) Conjunctivitis (COSTART term)

Severity	1. to 4. Mild
Serious (yes/no)	No
Start/stop date of event	1. 21 Jun 2001 until 25 May 2002
	2. 16 Nov 2001 until ongoing
	3. 26 Nov 2001 until 03 Jun 2002
	4. 28 Nov 2001 until 06 Mar 2002
Date of last dose of study drug before event	1. 21 Jun 2001
	2. 14 Nov 2001
	3. 25 Nov 2001
	4. 25 Nov 2001
Action taken	1. and 2. None
	3. and 4. Remedial drug therapy
Outcome of event	1. to 4. Resolved
Relationship to study drug	1. Probable
	2. to 4. None

Narrative:
This patient who was 65 years old when he received study medication for the first time had a history of diabetes mellitus type II since 1994, microhematuria since 1998 and benign prostatic hypertrophy since 1999. Concomitant medication included Glucophage (metformin) for diabetes since 1994 and multivitamin since Apr 2001. Laceration of right eye and eye infection occurred on day 534 of treatment and were treated with Quixin (levofloxacin) and refresh tears from 28 Nov 2001 ongoing first as treatment until resolution and afterwards for prophylaxis. He had a pinguecula of both eyes from day 525 of treatment onwards. These events were assessed as not related to study medication. There were several episodes of visual blue tint spots occurring after intake of study medication and resolved without any further action, which were assessed as probably drug related. The patient completed the study.

Reviewer's Comments: *There is a contradiction in the report. The stop date of event 2 is listed as ongoing. The outcome is listed as resolved.*

Patient identifier 010573-903-0194 **Date of birth** 1942
Sex M **Height (cm)** 180 **Baseline weight (kg)** 81
Race Caucasian **Study drug** BAY 38-9456 10 mg
Start/stop dates of study drug 09 Jul 2000 (Study 010125) until 28 Jun 2002
Event Blurred vision (Investigator term) Amblyopia (COSTART term)
Severity Mild
Serious (yes/no) No
Start/stop date of event 10 Jan 2002 until ongoing after end of study
Date of last dose of study drug before event 10 Jan 2002
Action taken None
Outcome of event Worsened
Relationship to study drug Probable
Narrative:
This patient who was 44 years old when he received study medication for the first time had a medical history of bilateral varicocele with embolization on the left side in 1995 and large testes left side with suspect of inguinal hernia since 29 May 2001. Since July 2001 he reported until end of study flushing, hives (these conditions were of mild intensity and apart from flushing not assessed as drug related and remained unchanged throughout the study period with no action taken) and warts of the penis as well as fatigue of mild intensity since August 2001, which resolved at end of study and was not assessed as drug related. Concomitant medication taken during this extension study included Entrophen (acetylic salicylic acid) 1 tablet daily, Propecia (finasteride) 1 tablet daily, both drugs since 1998, Effexor (venlafaxine) from 26 Jun 2000 until 20 Jan 2002 (Day 561 of treatment), Paramex 1 tablet daily from Day 352 of treatment onwards until the end of study. On day 551 of treatment the patient reported blurred vision after intake of study medication, which lasted beyond the study period. A probable relationship to study medication was assessed by the investigator. The patient completed the study.

Reviewer's Comments: *The use of the term amblyopia is incorrect. It is not clear why this event did not resolve. An etiology of the blurred vision should be determined.*

Patient identifier 010573-010-0011 **Date of birth** 1946
Sex M **Height (cm)** 185 cm **Baseline weight (kg)** 82 kg
Race Caucasian **Study drug** BAY 38-9456 20 mg

Start/ stop dates of study drug	1. 28 May 2000 to 09 Jun 2001 (010125) 2. 12 Jun 2001 to 15 Jun 2002 (010573)
Event	1. Burning eyes 2. Blue vision (two times)
Severity	Mild
Serious (yes/no)	No
Start/stop date of event	1. 30 Aug 2000 to 09 Jun 2001 2. 12 Jun 2001 to 08 Sep 2001
Date of last dose of study drug before event	1. 29 Aug 2000 2. Not known
Action taken	None
Outcome of event	Resolved
Relationship to study drug	1. Possible 2. None

Narrative

This patient has a history of hyperlipemia since 28 Mar 2000. He had taken sildenafil (oral, 50 mg, on demand) in the period from 28 Mar 2000 to 20 Apr 2000. In addition to study medication he took atorvastatin (oral, 10 mg daily) since 17 Apr 2000. He was randomized (Visit 2) on 23 May 2000.

1. At Visit 5 (30 Aug 2000) he reported about burning eyes. There is no further information about concomitant medication available, nor is there any further medical information about .eye pain. (reported symptom). The investigator classified the relation to the study drug as possible and the severity as mild. The patient remained in the study.
2. At Visit 9 (10 Sep 2001) in Study 010573 the patient reported that he had two episodes of blue vision of mild severity between last study visit and Visit 9. He could not give the exact dates when he had those two episodes of blue vision. Therefore these events could not be correlated to study drug intake. The investigator judged the event as unrelated to study drug.

Reviewer's Comments: *The instructions to the investigator concerning classifying an event as related or not related should be reviewed. It is not clear how the investigator could consider two events of "blue vision" occurring between study visit dates as being unrelated to the study drug just because the exact dates could not be ascertained.*

Labeling: *(Only sections relevant to ophthalmic findings are listed in this review)*

This reviewer's proposed additions are identified by double underlining. Proposed deletions are identified by single line strikeouts.

LEVITRA™ (vardenafil HCl tablets)

Pharmacodynamics

Draft

Reviewer's Comments: *The one year study identified was problematic as identified earlier in this review. It is not supportive of the proposed statements. The statements supported by the single dose studies have been revised to reflect the findings in ERG and Farnsworth-Munsell testing.*

APPEARS THIS WAY
ON ORIGINAL

WARNINGS

...

The safety of vardenafil has not been studied in the following subgroups of patients, and its use is therefore not recommended until further information is available: severe hepatic impairment; end stage renal disease requiring dialysis; unstable angina; hypotension (resting systolic blood pressure of <90 mmHg); uncontrolled hypertension (>170/110 mmHg); recent history of stroke, life-threatening arrhythmia, or myocardial infarction (within the last 6 months); severe cardiac failure; and known hereditary degenerative retinal disorders including but not limited to retinitis pigmentosa.

...

Reviewer's Comments: *Retinitis pigmentosa is just one of many degenerative retinal disorders which would potentially be affected*

ADVERSE REACTIONS

...

The following section identifies additional, less frequent events reported during the clinical development of LEVITRA. It is important to emphasize that although the events reported in the list below occurred during treatment with vardenafil, they were not necessarily caused by it. The list identifies reported events by body system that may be useful to clinicians when making treatment decisions, monitoring, and advising patients. Excluded from this list are those events which are infrequent and minor, those events which may be commonly observed in the absence of drug therapy, and those events which are not reasonably associated with the drug.

Special Senses: abnormal vision, blurred vision , chromatopsia, changes in color perception, conjunctivitis (increased redness of the eye), dim vision, eye pain, glaucoma, photophobia, watery eyes

...

Reviewer's Comments: *Amblyopia is a condition with an onset in childhood. The additional terms have been added as clarification of terms reported in the clinical studies.*

Regulatory Recommendation:
It is recommended that the labeling be revised as identified in this review prior to approval. It is recommended that additional Phase 4 studies be conducted to evaluate the potential effect on visual function of repeated drug administration.

There are many events listed in the Safety Update which deserve further follow-up. In addition to the labeling comments, the following comments should be relayed to the applicant:

In Study 10125, there are multiple problems in the reporting of ophthalmologic data. Specifically:

1. There are very limited numbers of patients with individual ophthalmologic examinations (rarely more than 70 patients for any specific ocular examination). Less than 50 patients per group are evaluated at Week 13 for Lens and less than 30 per group at Week 13 for ERG. Even less ocular examination data is available at Week 52.
2. It is not clear what scoring system was used for the FM100 since the traditional scoring system for the FM100 includes only even integers.
3. The 20 mg group appears to demonstrate decreased color vision. Normal testing would have been expected to demonstrate improvement in the scores because of the learning curve routinely observed with this color vision test.
4. Reported visual acuities of 0, 151, 153, 201 and 203 are not consistent with the equipment used to measure visual acuity.
5. The N (number of patients evaluated) cannot be approximately the same in the right and left eye since the "N Missing" values vary between eyes by over 50 observations.
6. Abnormal findings in the ERG were reported in between 12 and 25% of the patients.
7. Abnormal findings in the fundus were reported in between 4 and 12% of the patients.
8. Abnormal findings in the lens were reported in between 6 and 25% of the patients.
9. Abnormal findings in the slit lamp exam were reported in between 1 and 11% of the patients.

In the safety update, there are questions about the following patients:

010573-120-0002: Why was nystagmus not considered a serious adverse event? The patient should continue to be followed for a cause of the nystagmus.

010573-101-0374: Macular holes are highly unlikely to resolve without any further action. What was the visual acuity upon resolution?

010573-120-0035 There is a contradiction in the report. The stop date of event 2 is listed as ongoing. The outcome is listed as resolved. This contradiction should be clarified.

010573-903-0194 The term amblyopia is incorrect. It is not clear why this event did not resolve. An etiology of the blurred vision should be determined.

010573-010-0011 The instructions to the investigator concerning classifying an event as related or not related should be reviewed. It is not clear how the investigator could consider two events of "blue vision" occurring between study visit dates as being unrelated to the study drug just because the exact dates could not be ascertained.

/S/

Wiley A. Chambers, MD
Supervisory Medical Officer, Ophthalmology

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/s/

Wiley Chambers
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MEDICAL OFFICER

Wiley Chambers
7/22/03 02:04:38 PM
MEDICAL OFFICER
Only final version of labeling recommendations are visible in this document. Export this review to Word to see how the original was revised.

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Consultative Clinical Review

NDA: 21-400 (vardenafil)

Sponsor: Bayer

Submission: The Division of Cardio-Renal Drug Products is asked to comment on effects of vardenafil on QT.

Review date: June 25, 2002

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Concurrence: DC Throckmorton, MD, Division Director

Summary: Vardenafil is a new molecular entity, currently under NDA review in DRUDP for the treatment of erectile dysfunction. Although the available data raise no concern regarding arrhythmogenic potential, the data are not particularly compelling that such a risk has been ruled out.

Distribution: NDA 21-400

HFD-580/Project Manager

HFD-580/Benson

HFD-580/Hirsch

HFD-580/Shames

Vardenafil is a PDE-5 inhibitor, with a mechanism of action similar to that of sildenafil.

The majority of the safety data come from 3872 subjects in phase 3 trials of erectile dysfunction, receiving placebo (n=793) or doses of 5 to 20 mg. There is very little experience with doses above 20 mg, which is the highest dose the sponsor contemplates marketing.

Doses above 20 mg are associated with back pain and myalgia, said to be severe and self-limiting.

Adverse events in man are the most definitive indication of arrhythmogenic risk, so these are considered first. There is only one moderately suspicious death:

Subject "10125_1110_342 was a 69-year-old man with a history of hypertension and diabetes mellitus who completed the first 6 visits of the randomized treatment period without any problems and was due for the seventh visit on Day 253. Before the seventh visit, the patient's partner notified the study coordinator that the patient had passed away on Day 246. He apparently died in his sleep and was found unresponsive at home. An autopsy was performed, and the death was probably attributed to complications of cardiovascular disease secondary to diabetes mellitus and hypertension. "

Torsade de pointes is usually not fatal, and it can manifest itself as unexplained syncope. However, this is a particularly unreliable indicator of risk if, as in this case, the agent lowers blood pressure or causes some other alternative effect producing

syncope. The sponsor reported only 4 cases of syncope in placebo-controlled studies, the rate being insignificantly different on active drug. Another 6 cases occurred during open-label studies, some resulting in subject discontinuation, but all such cases were in subjects with complex cardiovascular disease and none of these cases occurred very near the time of peak plasma levels following a dose.

QT data were available for 4 studies involving normal volunteers and doses of 40 or 80 mg. At the request of the Agency, the sponsor provided machine-readable ECG data for 2 studies in subjects with erectile dysfunction; one of these studies utilized a dose of 40 mg.[1]

In Study 94, 45 normal volunteers were randomized 1:2 to single oral doses of placebo or vardenafil 5, 10, 20, 40, or 80 mg, and ECGs were collected at baseline and after 1, 2, 3, 4, 6, 8, 12, and 24 hours. The figure shows the distribution of QT vs. HR for all subjects at baseline or placebo subjects at any time (0 mg) and for the 1 to 2 hour times following the 80-mg dose. Although the mean heart rate appears to be increased at 80 mg, the relationship between QT and HR is very similar on 0 and 80 mg. This is the only study utilizing 80 mg and collecting ECGs.

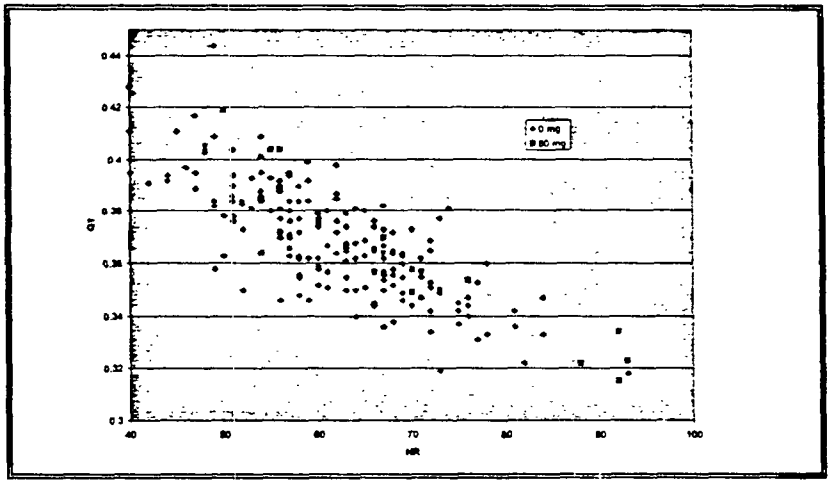

Figure 1. QT vs. HR for Study 94

In Studies 10010 and 10011, a total of 42 subjects with erectile dysfunction received, in random order, single oral doses of placebo and vardenafil 10 and 20 mg (10010) or 20 and 40 mg (10011), and ECGs were obtained at baseline and after 2.5, 4, 6, 12, and 24 hours. QT values are, if anything, somewhat lower on average at 40 mg than at baseline or on placebo. These are the only studies in subjects with erectile dysfunction with ECGs performed near the time of peak plasma levels.

[1] *QT data from the phase 3 studies are much less helpful, in that ECGs were obtained an indeterminate (but long) time after a dose.*

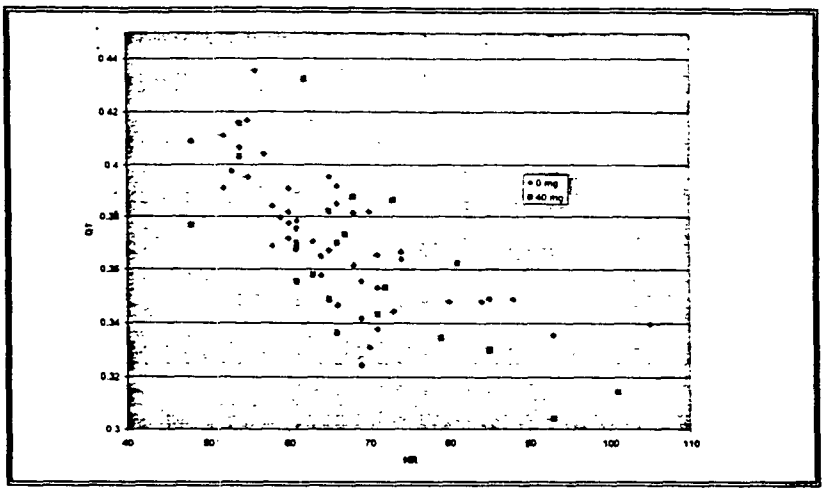

Figure 2. QT vs. HR for Studies 10010 and 10011.

In Study 100195, 48 normal volunteers were randomized 1:3 to single oral solutions of placebo or vardenafil 40 mg, and ECGs were performed at baseline and after 0.5, 1, 2, 4, and 8 hours. The figure shows the relationship between QT and heart rate for subjects at zero dose (placebo or baseline) and after 30 minutes to 2 hours after the 40-mg dose.

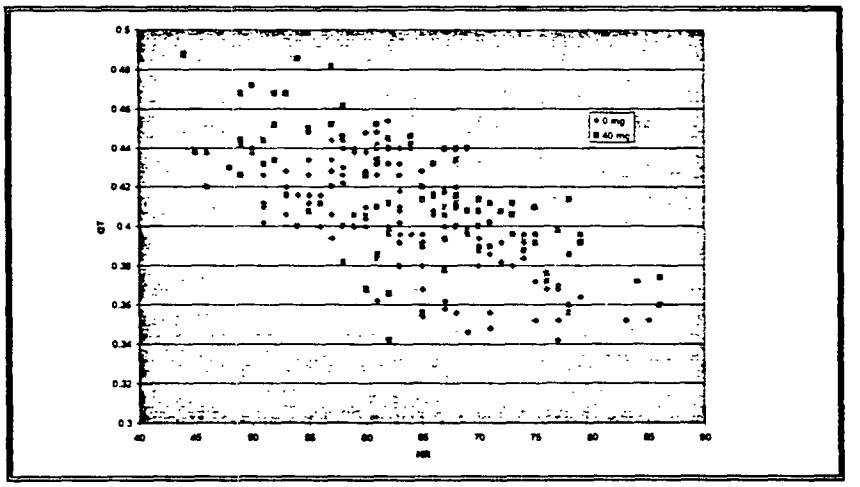

Figure 3. QT vs. HR for Study 100195.

In Study 100196, 50 normal volunteers were randomized to placebo or vardenafil 20 mg daily, 40 mg daily, or 40 mg every other day for 31 days, and ECGs were performed at baseline and 2, 4, 8, and 24 hours after the first and last doses. The figure shows the relationship between QT and heart rate for subjects at zero dose (placebo or baseline) and after 2 hours on the 40 mg dose at visits 1 or 31.

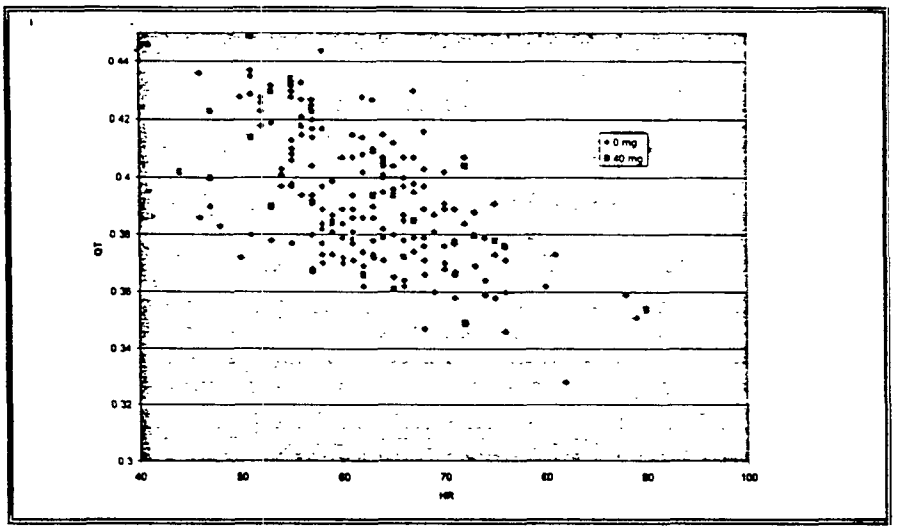

Figure 4. QT vs. HR for Study 100196.

In Study 10006, 25 normal volunteers were randomized 1:2 to placebo or vardenafil 40 mg qd or 40 mg bid, for 14 days, and ECGs were performed at baseline and 1, 2, 3, 4, 6, 9, 11, and 24 hours after the last dose. The figure shows the relationship between QT and heart rate for subjects at zero dose (placebo or baseline) and 1 or 2 hours after the last dose (usually day 14).

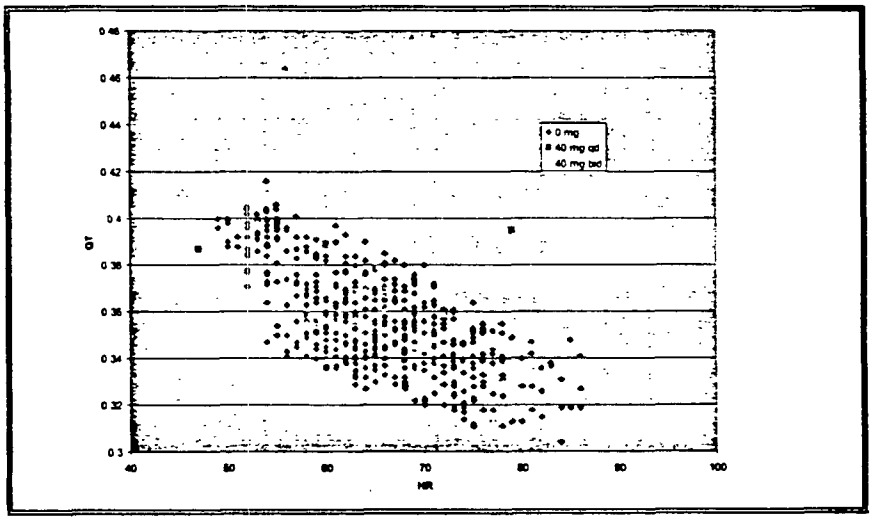

Figure 5. QT vs. HR for Study 10006

The sponsor analyzed changes in QT, QTcB, and QTcF in these same studies, as shown in Figure 6.

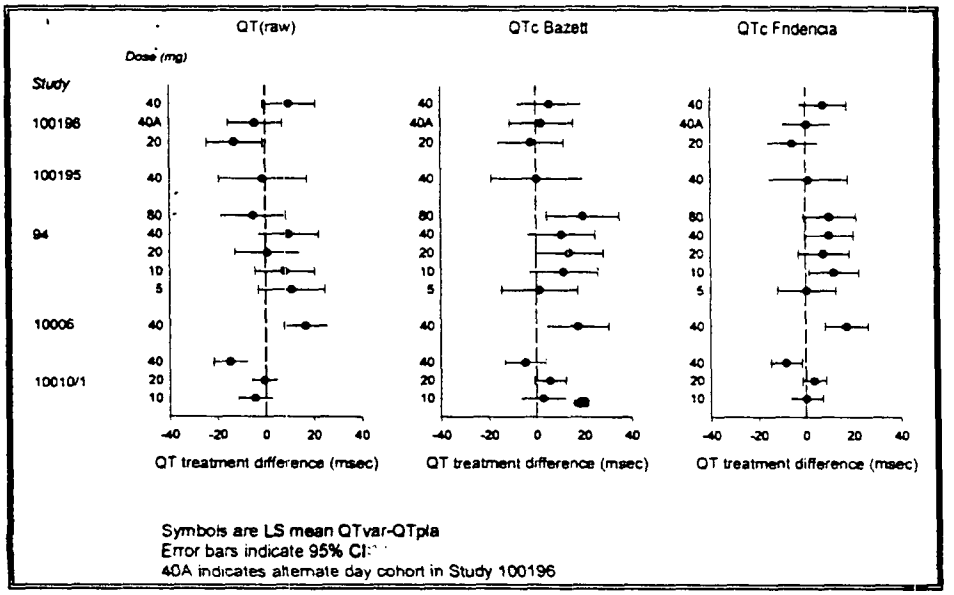

Figure 6. QT data for all studies

Sponsor's analysis (page 194 of Integrated Summary of Safety). Values are changes from placebo, apparently not double-differences from baseline and placebo.

By the sponsor's analysis, doses >20 mg may have a small increase in QT.

As part of this review, the data from the placebo, 40-mg, and 80-mg groups were pooled and analyzed for the distribution of changes in QTcF from baseline to the time closest to 1 hour (up to 2.5 hours) after the last available on-treatment dose. These data are shown in Figure 7. Positive changes are increases from baseline.

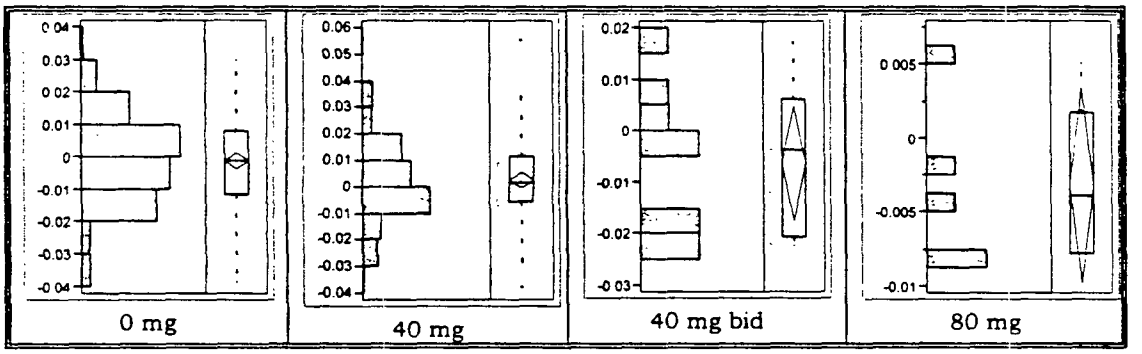

Figure 7. Distribution in changes from baseline in QTcF.

By this analysis, there appears to be no increase in QTcF at 40 or 80 mg. There is no mean increase and no 'tail' to the distribution in the positive direction.

Vardenafil was shown to block HERG channels reconstituted in HEK293 cells, to a degree and with a potency similar to that of sildenafil.

With exposure (plasma levels) 250-times higher than achieved with 20-mg doses in man, vardenafil had no discerned effect on QTcB in the dog.

In summary, what data there are raise no particular anxiety regarding arrhythmogenic potential, and having nuisance symptoms limiting dose, if they do, is reassuring—higher doses, which were less adequately studied, are unlikely to see much use.

In many respects the amount of data and what the data say resemble the data from a previous consult for another PDE-5 inhibitor.

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/s/

Norman Stockbridge
6/25/02 08:19:59 AM
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Doug Throckmorton
7/3/02 08:20:41 AM
MEDICAL OFFICER

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

NDA 21-400
Ophthalmology Consult

Submission date: 9/24/01

Review date: 6/24/02

Sponsor: Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
(203) 812-3051

Contact: Gautam Shah, Ph.D.

Drug Product: (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
Clinical Studies
10197
100196
Proposed package insert labeling
Integrated Summary of Safety

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.

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

Two clinical studies evaluating vision were performed with vardenafil. Each study demonstrates 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.

Protocol 10197
Protocol 100196

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 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 pass 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 total error score 1 and 6 hours after drug administration and for error score line 3 and line 4, with one hour having 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: *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	SD	MIN	MEDIAN	MAX	FS(FS) MEAN	SD	MIN	MEDIAN	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, but the power to demonstrate a difference is small and it was 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 b wave amplitudes. There does not appear to be an effect on intraocular pressure. There is not sufficient power in the study to evaluate the potential effect on visual acuity or visual field.

Title of the study: 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 [100196]

Investigator(s): Thomas L. Hunt, MD, PhD and Krishna Talluri, MD
Study center(s): Center 01 Austin, TX
Center 02 Morrisville, NC

Period of study: 16 February 1999 - 17 May 1999

Clinical phase: Phase 1

Objectives: The primary objective of this study was to determine the safety and tolerability of multiple-dose treatments of BAY 38-9456 in dosages up to 40 mg daily for 31 days in healthy middle-aged and elderly male subjects. The secondary objective was to define the multiple-dose pharmacokinetics of BAY 38-9456 and BAY 44-5576 (M-1, the expected main metabolite).

Methodology: This study was a randomized, double-blind, placebo-controlled, parallel-group trial of orally administered BAY 38-9456 in healthy middle-aged and elderly male subjects. Subjects were randomly assigned to 1 of 4 treatment groups: 20 mg BAY 38-9456 (QD) (12 subjects), 40 mg BAY 38-9456 QD (13 subjects), 40 mg BAY 38-9456 every other day (QOD) alternating with placebo (13 subjects), or placebo (12 subjects) QD. Subjects were screened within 3 weeks prior to receiving the first dose of study drug on Day 1. Screening included the following: complete medical history and physical examination, including height and weight; vital signs; color vision testing; PA and lateral chest X-ray; clinical laboratory tests including hematology, blood chemistry and urinalysis, hepatitis, and urine drug screens, and a serum TSH, T_3, and T_4 if a subject was receiving thyroid hormone replacement.

Reviewer's Comments: *Patients were required to be "In good health, as judged by both the investigator and sponsor, as evidenced by medical history, physical examination findings, clinical laboratory evaluation, electrocardiogram, chest x-ray and color vision testing." This was not always the case, as some patients (100196-001-1014, 1028, 1055; 100196-002-2046) had abnormal color vision at the screening visit. One patient had trauma (100196-001-1062, hit in left eye by tree branch) three days before the screening and is reported as recovering during the study. Patient 100196-001-1024 had a macular scar noted at screening.*

Subjects entered the clinic on the evening of Day –2. On the morning of Day –1, a 24-hour urine collection began for evaluation of liver enzyme induction. Subjects began fasting from 10 PM on the evening of Day –1 and continued to fast until 4 hours after dosing on Day 1. On the morning of Day 1, subjects received 20 mg BAY 38-9456 QD, 40 mg BAY 38- 9456 QD, 40 mg BAY 38-9456 QOD alternating with placebo, or matching placebo QD. Subjects were not allowed to drink for 2 hours before dosing, and they fasted for 4 hours after dosing.

A standard lunch was served 4 hours after dosing. On Day 1 and Day 31, plasma samples were collected for the determination of BAY 38-9456 and BAY 44-5576 predose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours after dosing. A plasma sample was collected at 30, 36, and 48 hours after dosing on Day 31. On Day 8 and Day 14, a trough plasma sample was collected predose. On Day 1 and Day 31, urine was collected in separate containers for possible future analysis of drug and metabolites at the following intervals: 0-4 hours, 4-8 hours, 8-12 hours, and 12-24 hours postdose. A predose urine "blank" was obtained on Day 1 only. A second 24-hour urine collection was done for evaluation of enzyme induction at steady state, beginning the morning of Day 30 and ending the morning of Day 31. Subjects were monitored for safety and tolerability throughout the study by physical and ophthalmology examinations, vital signs, ECG, and clinical laboratory tests. Approximately 7 and 30 days after the final dose on Day 31 (Day 38 and Day 61), the clinic staff contacted all subjects by telephone and conducted a Wellness Assessment.

Number of patients A total of 101 subjects were enrolled in the study and screened for eligibility; 50 subjects were randomly assigned to one of the 4 treatment groups. The 50 subjects were randomly assigned to study drug treatment as follows: placebo (12 subjects); 20 mg BAY 38-9456 QD (12 subjects); 40 mg BAY 38-9456 QOD (13 subjects); and 40 mg BAY 38-9456 QD (13 subjects). Forty-seven subjects completed the 31-day treatment period. Subjects ranged in age from 45 to 70 years, and in weight from 58.7 to 128.5 kg. The ethnic composition of the study population was 41 Caucasian, 6 Black, 1 American Indian, and 2 Hispanic.

Reason for Screen Failures	Number of Subjects
Protocol violation	32
Consent withdrawn	5
Sponsor/investigator exclusion	11
Lost to follow-up	2
Atrial bigeminy	1
Total	51

Source: Listing Section 16.2.10, Data Listing 21.

Selected Demographic and Baseline Characteristics				
		BAY 38-9456	BAY 38-9456	BAY 39-9456
	Placebo	20 mg QD	40 mg QOD	40 mg QD
Variable	(N=12)	(N=12)	(N=13)	(N=13)
Race, N (%)				
Caucasian	12 (100)	11 (92)	12 (92)	6 (46)
Black		1 (8)	1 (8)	4 (31)
American Indian				1 (8)
Hispanic				2 (15)
Mean age [years] (±std dev)	55.3 (6.7)	53.3 (8.2)	52.4 (6.3)	53.7 (8.1)
Range	47-70	45-66	45-64	45-68
Mean Weight [kg] (±std dev)	89.7 (15.5)	86.1 (12.1)	84.5 (10.1)	82.6 (9.0)
Range	70.8-128.5	69.0-107.7	68.4-100.8	58.7-93.1
Mean height [cm] (±std dev)	180.7 (8.0)	179.4 (7.1)	179.9 (5.9)	179.2 (7.5)
Range	164.1-193.0	167.6-191.0	170.2-190.5	161.0-188.0
Source: Section 14.1, Table 1				

During the 31-day treatment period, subjects took 20 mg BAY 38-9456, 40 mg BAY 38-9456, or placebo once daily. Study drug was administered in the morning between 7:00 AM and 10:00 AM. Immediately after ingesting study drug, subjects drank 180 mL of tap water. The dose was administered as 1 or 2 x 21.5 mL BAY 38-9456 0.1% oral solution or matching placebo solution. Study drug was packaged in bottles and each bottle contained 20 mg BAY 38-9456 base or matching placebo

Reviewer's Comments: *There are unfortunately errors in the database for the ophthalmic examinations. Final conclusions should not be drawn from this study until the database is corrected. For example: Patient 100196-001-1007 is listed as having a spherical refraction of 67 in each eye. It is highly unlikely that this is physiologically possible for anyone.*

Ophthalmic Testing:

Ophthalmic Testing included:

- Ocular symptoms
- Best corrected distance visual acuity
- Color vision (Ishihara)
- Visual fields (Amsler grid method)
- Gross External Examination
- Pupillary reaction
- Motility
- Slit Lamp Examination of anterior segment
- Intraocular Pressure (applanation)
- Dilated Ophthalmoscopy

Reviewer's Comments:

The use of an Ishihara examination for color vision is not appropriate because it does not detect common acquired defects in the blue-yellow discrimination area.

The use of Amsler grid for visual fields is not appropriate because it is not sufficiently sensitive to detect many changes in the visual field.

The study report states that there were no clinically significant changes detected on ophthalmic examination. There are no summaries of the ophthalmic information and it does not appear that any attempt was made to coordinate or review the information. There were numerous clinical findings reported in the examinations. Some of them are listed below.

Patient 100196-001-1008 had an elevation of IOP from 16 to 24 mmHg.
Patient 100196-001-1013 had ocular redness, puntate staining of the cornea and changes in the lens.
Patient 100196-001-1004 reported dimmer vision.
Patient 100196-001-1007 reported halo distortion.
Patient 100196-002-2045 reported red vision.
Patient 100196-002-2055 reported blue vision.
Patient 100196-002-2056 reported a blue tint in the background.

Two of 8 subjects who experienced visual changes on 40 mg BAY 38-9456 had blue color vision changes by ophthalmic exam near the time of C_{max}.

Pharmacokinetic Parameters for BAY 39-9456 on Days 1 and 31

Parameter[a]	20 mg QD (n=12)[b]	40 mg QOD (n=13)	40 mg QD (n=13)
Day 1			
AUC_{0-24} (µg*h/L)	70.1 (39%)	130.3 (47%)	136.6 (52%)
$AUC_{0-\infty}$ (µg*h/L)	71.5 (40%)	132.5 (48%)	138.7 (53%)
C_{max} (µg/L)	17.0 (41%)	29.5 (48%)	30.9 (53%)
T_{max} (h)	0.9 (36%)	0.9 (44%)	1.3 (48%)
t½ (h)	4.2 (37%)	4.2 (39%)	4.2 (30%)
Day 31			
AUC_{0-24} (µg*h/L)	75.7 (47%)	127.2 (56%)	139.0 (52%)
C_{max} (µg/L)	16.6 (47%)	30.2 (45%)	31.0 (50%)
T_{max} (h)	0.9 (41%)	1.0 (47%)	1.1 (32%)
t½ (h)	5.1 (34%)	4.6 (32%)	4.8 (41%)
AR[c], AUC (%)	111.4 (30%)	97.6 (25%)	100.3 (22%)
AR, C_{max} (%)	99.4 (31%)	102.4 (38%)	98.8 (30%)

[a]Presented as geometric mean (coefficient of variation)
[b]n=11 for Day 31
[c]AR = accumulation ratio

Treatment-Emergent Adverse Events Reported by at least 2 Subjects in a Treatment Group

		BAY 38-9456		
COSTART Term	Placebo (n=12)	20 mg QD (n=12)	40 mg QOD (n=13)	40 mg QD (n=13)
Any Event	6 (50%)	10 (83%)	12 (92%)	12 (92%)
Headache	1 (8%)	6 (50%)	6 (46%)	7 (54%)
Back pain	0 (0%)	3 (25%)	3 (23%)	7 (54%)
Asthenia	1 (8%)	3 (25%)	2 (15%)	1 (8%)
Pain	1 (8%)	2 (17%)	2 (15%)	2 (15%)
Leg pain	1 (8%)	3 (25%)	2 (15%)	1 (8%)
Neck rigidity	0 (0%)	0 (0%)	0 (0%)	2 (15%)
Accidental injury	2 (17%)	0 (0%)	0 (0%)	0 (0%)
Vasodilatation	1 (8%)	1 (8%)	2 (15%)	0 (0%)
Dyspepsia	2 (17%)	4 (33%)	3 (23%)	5 (38%)
Diarrhea	1 (8%)	1 (8%)	2 (15%)	4 (31%)
Myalgia	0 (0%)	1 (8%)	2 (15%)	2 (15%)
Dizziness	0 (0%)	2 (17%)	3 (23%)	2 (15%)
Somnolence	2 (17%)	0 (0%)	0 (0%)	0 (0%)
Rhinitis	2 (17%)	1 (8%)	1 (8%)	2 (15%)
Rash	0 (0%)	0 (0%)	2 (15%)	0 (0%)
Pruritus	0 (0%)	0 (0%)	2 (15%)	0 (0%)
Abnormal vision	0 (0%)	0 (0%)	3 (23%)	4 (31%)
Photophobia	0 (0%)	0 (0%)	2 (15%)	1 (8%)
Amblyopia	1 (8%)	0 (0%)	2 (15%)	0 (0%)
Conjunctivitis	2 (17%)	1 (8%)	0 (0%)	1 (8%)
Erections increased	0 (0%)	0 (0%)	2 (15%)	4 (31%)
Priapism	0 (0%)	0 (0%)	2 (15%)	0 (0%)
Urinary frequency	0 (0%)	0 (0%)	2 (15%)	0 (0%)

Source: Section 14.3.1, Table 1

Sponsor's Conclusions:
There was no apparent relationship between BAY 38-9456 dose group and individual events except for back pain, diarrhea, and abnormal vision. Three subjects in the BAY 38-9456 20 mg QD group (25%) and the 40 mg QOD group (23%) reported back pain compared with 7 (54%) subjects in the 40 mg QD group. One (8%) subject in the BAY 38-9456 20 mg QD group and 2 (15%) subjects in the 40 mg QOD group reported diarrhea compared with 4 (31%) subjects in the 40 mg QD group. None (0%) of the subjects in the BAY 38-9456 20 mg QD group reported abnormal vision compared with 3 (23%) subjects in the 40 mg QOD group and 4 (31%) subjects in the 40 mg QD group. The color vision abnormalities were confirmed in only 2 of these subjects on interim ophthalmic examination.

Reviewer's Conclusions concerning study 100196

This study is of little value because:

1. *It included patients in violation of the inclusion criteria which were important in assessing changes in vision.*
2. *It used tests which were not sufficiently sensitive to detect changes.*
3. *It failed to identify observed changes from baseline.*
4. *It included only a small number of patients.*
5. *The database did not appear to be correctly entered, so it is not possible to determine which values are correct.*

Treatment Emergent Adverse Events Related to the Eye or Vision (Pool 3)

Visual Event	Placebo (N = 793)	Vardenafil (N = 1812)
Conjunctivitis	2 (0.3%)	16 (0.9%)
Abnormal vision	2 (0.3%)	11 (0.6%)
Amblyopia	1 (0.1%)	7 (0.4%)
Photophobia	0 (0.0%)	7 (0.4%)
Eye hemorrhage	0 (0.0%)	5 (0.3%)
Lacrimation disorder	0 (0.0%)	5 (0.3%)
Cataract specified	0 (0.0%)	4 (0.2%)
Eye pain	0 (0.0%)	3 (0.2%)
Dry eyes	0 (0.0%)	2 (0.1%)
Glaucoma	0 (0.0%)	2 (0.1%)
Chromatopsia	0 (0.0%)	1 (<0.1%)
Corneal lesion	0 (0.0%)	1 (<0.1%)
Eye disorder	0 (0.0%)	1 (<0.1%)
Mydriasis	0 (0.0%)	1 (<0.1%)
Refraction disorder	0 (0.0%)	1 (<0.1%)
Retinal disorder	0 (0.0%)	1 (<0.1%)
Retinal hemorrhage	0 (0.0%)	1 (<0.1%)
Blindness	1 (0.1%)	0 (0.0%)
Vitreous disorder	1 (0.1%)	0 (0.0%)

Pool 3, Table 2/1.1

There were 3 special senses adverse events that led to premature discontinuation in the vardenafil group compared to none in the placebo group. These events were abnormal vision (1), conjunctivitis (1), and lacrimation disorder (1). There were no serious adverse events related to eye symptoms or vision in either placebo or vardenafil treatment groups.

Sponsor's summary

In summary, vardenafil treatment was associated with a low incidence of adverse events related to vision and eye complaints and most of these were of mild intensity. Most patients who experienced these side effects continued on treatment, and serious visual adverse events related to treatment were not observed. In Clinical Pharmacology studies doses higher than those tested in the Phase III clinical trials resulted in changes of color vision in the blue/green hue range. These changes were most pronounced by 1 hour, improved by 6 hours, and had resolved by 24 hours after dosing. The transient change in color vision is associated with a mild reduction of the cone driven b-wave amplitude. However, color vision change was reported rarely (<0.1%) with vardenafil treatment in the clinical studies.

2 pages redacted from this section of the approval package consisted of draft labeling

Regulatory Recommendation:

It is recommended that the labeling be revised as identified in this review prior to approval. It is recommended that additional Phase 4 studies be conducted to evaluate the potential effect on visual function of repeated drug administration.

/S/

Wiley A. Chambers, MD
Supervisory Medical Officer, Ophthalmology

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/s/

Wiley Chambers
6/25/02 12:50:17 PM
MEDICAL OFFICER

Wiley Chambers
6/25/02 12:56:24 PM
MEDICAL OFFICER

Safety Update

Please refer to the Medical Officers Reviews.