Appendix A- Clinical Trial 10929: "A study to evaluate the effect of a range of single oral doses of vardenafil and sildenafil on cardiac conduction as assessed by 12-lead electrocardiogram as compared to placebo and moxifloxacin" (Trial start: August 26, 2002; trial completion: October 1, 2002). Study sites: Philadelphia, Pennsylvania and Austin, Texas.

A.1 Objectives:

Primary: To rule out a greater than 10 msec effect (i.e. to demonstrate lack of effect) of a single 80 mg oral dose of vardenafil on QTc interval as compared to placebo, as measured by the change from baseline at the 1 hour post-dose time point.

Secondary:

(1) To characterize the effect of a single 80 mg oral dose of vardenafil on QTc interval as compared to placebo, as measured by the change from baseline at the time of maximum concentration (Tmax).

(2) To characterize the effect of a single oral dose of 400 mg of moxifloxacin on QTc interval relative to placebo.

(3) To characterize the effect on QTc relative to placebo of single oral doses of 10 mg of vardenafil and of 50 and 400 mg of sildenafil.

(4) To characterize the effect on QT and HR relative to placebo of single oral doses of 400 mg of moxifloxacin, 10 and 80 mg of vardenafil and of 50 and 400 mg of sildenafil.

(5) To characterize the pharmacokinetics of vardenafil, sildenafil and moxifloxacin.

(6) To explore the relationship between vardenafil, sildenafil and moxifloxacin exposure versus ECG parameters (QTc, QT intervals and HR).

A.2 Design and conduct summary: This study was a double-blind, randomized, single dose, 6-way crossover, period-balanced study in healthy adult males. Each subject participated in 6 study sessions separated by a minimum washout period of at least 3 days. Each subject received the following six regimens in a randomized crossover fashion. (AFBECD, BACFDE, CBDAEF, DCEBFA, EDFCAB, or FEADBC)

Table A.1 Regimen description

Regimen	Regimen Description
A	Vardenafil 10 mg
B	Vardenafil 80 mg
C	Sildenafil 50 mg
D	Sildenafil 400 mg
E	Moxifloxacin 400 mg
F	Placebo

Source: Study report 10929, page 11.

Prior to study drug administration, a screening period consisted of a complete medical history and physical exam, medication history for 30 days prior to screening, standard 12-lead ECG, supine BP and pulse rate, blood and urine specimens and urine drug/alcohol screen. Clinical laboratory tests performed included hematology, serum biochemistry, urinalysis, Hep B/C and HIV screening.

Treatment phase: Subjects checked-in the night before or by 7 a.m. on Day 1 of each period. Subjects remained in the research facility for a minimum of 20-24 hours and then returned after a 3-day washout for the next session. Study medication was administered with 240 cc of tepid water by an individual not involved with the study to maintain the double-blind. The subjects were blind-folded prior to receiving the study medication.

Safety: Safety was assessed by 12-lead ECGs, blood pressure/pulse rate measurements, adverse events and clinical laboratory safety tests. Supine ECGs were performed at time -0.5, -0.25, predose, 0.5, 1, 1.5, 2.5 and 4 hours. ECGs were manually read and confirmed by a high-resolution digitizing pad system. All ECGs were read blinded. Patients were not dosed if the pre-dose ECG showed either PR interval > 240 msec or ≤ 110 msec; or QTc > 440 msec. Blood samples for pharmacokinetic analysis of vardenafil, sildenafil and moxifloxacin were collected from each subject at times 0, 0.5, 1, 1.5, 2.5, and 4 hours following single oral administration on Day 1 of each period.

Reviewer's comment: The correction method for QTc was not given in the protocol.

Restrictions: 1) Subjects fasted at least 4 hours prior to any clinical safety laboratory evaluations and 8 hours prior to start of the PK/PD collections. 2) Use of caffeine, alcohol, and tobacco were prohibited. 3) No strenuous activity was permitted from 48 hours prior to session 1 through study completion. Subjects remained on bed rest until ECG and lab assessments were completed.

A.3 Study population: Healthy adult male subjects between 45 and 60 years of age, and a body mass index of less than 35 kg/m^2 were eligible for the study. A sufficient number of subjects (approximately 72 subjects) were to be enrolled so that a total of 54 subjects completed the study. A total of 60 subjects were enrolled. One subject withdrew prior to dosing. Data from 59 subjects are included in the statistical analysis.

Table A.2 Demographics

Parameter	Age (years)	Height (m)	Weight (kg)
n	59	59	59
Mean	53	1.79	87.3
SD	4.3	0.07	13.8
Range	45-60	1.65-2.02	63.8-114.7

100% male, 12% Black; 81% White; 7% Hispanic

Source: Study report 10929, page 14

A.4 Inclusion and exclusion criteria:

Inclusion criteria:

(1) Healthy adult male subjects between 45 and 60 years of age, inclusive, at screening.

(2) Body mass index (BMI) <35 kg/m^2

(3) Negative for HIV, Hepatitis B and Hepatitis C at screening.

(4) Written informed consent.

Exclusion criteria:

(1) Any clinically relevant abnormality identified on the screening medical assessment, laboratory examination or 12-lead ECG.

• cardiac conduction abnormalities denoted by any of the following:
    - QTc interval > 440 msec
    - PR interval > 240 msec or ≤110 msec
    - Evidence of second- or third- degree atrioventricular (AV) block
• pathological Q-waves (defined as Q-wave > 40 msec or depth greater than 0.4-0.5 mV)
• evidence of ventricular pre-excitation
• electrocardiographic evidence of complete left bundle branch block, right bundle branch block (RBBB), incomplete RBBB

(2) History of lightheadedness or syncope upon standing.
(3) Subjects with a positive urine test for drugs of abuse or alcohol at screening.
(4) History of regular alcohol consumption exceeding 14 drinks/week (average) for men (1 drink = 5 ounces of wine or 12 ounces of beer or 1.5 ounces of hard liquor) within 6 months of screening.
(5) Prior treatment with sildenafil.
(6) History of epilepsy or other seizure disorders.
(7) History of glaucoma.
(8) Treatment with an investigational drug within 30 days or 5 half-lives (whichever was longer) preceding the first dose of study medication.
(9) Use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements within seven days or 5 half-lives (whichever was longer) prior to the first dose of study medication. By exception, acetaminophen (2 g/day) was permitted during the study.
(10) Known history of allergy to drugs, specifically PDE5 inhibitors.
(11) History of hypersensitivity to moxifloxacin or any member of the quinolone class of antimicrobial agents.
(12) Consumption of grapefruit or grapefruit juice within seven days prior to the first dose of study medication.
(13) History of sensitivity to heparin or heparin-induced thrombocytopenia.
(14) Blood collection of greater than 500 mL within 56 days prior to study start.

Reviewer's comments: 1) The correction method for QTc was not given in the protocol. 2) The inclusion and exclusion criteria are acceptable.

A.5 Primary and secondary endpoints:

Pharmacodynamic parameters: Six 12-lead ECGs taken approximately 1 minute apart were obtained at specified times (-0.5, -0.25, predose, 0.5, 1, 1.5, 2.5, and 4 hours). The primary pharmacodynamic parameter was manually read QTc intervals. **Fridericia's correction formula ($QTcF=QT/RR^{1/3}$) was used to correct for heart rate. The primary endpoint was the change from baseline at 1 hour post-dose.** The statistical analysis the primary endpoint was to rule out a greater than 10 msec effect of vardenafil 80 mg on QTc with an upper confidence interval of 90%. Secondary endpoints included change from baseline at the time of maximum concentration (Tmax), raw QT intervals and heart rate, as well as, individually corrected QT intervals (QTci). QTci is calculated using the formula QTci = QT + [b*(1-RR)]. The variable "b" was obtained from fitting each subject's data into the linear regression model QT= a + b * RR, where RR=60/HR.

Exploratory endpoints included maximum change from baseline and time averaged change from baseline.
Pharmacokinetic parameters: The relationship between effect (QTcF, msec) and plasma concentration was explored graphically following single oral administration of vardenafil (10 and 80 mg), sildenafil (50 and 400 mg) and moxifloxacin (400 mg). The plasma concentration-effect (PK/PD) relationship for vardenafil and sildenafil was characterized by a direct effect Emax model while that for moxifloxacin was described by a slope-intercept model using NONMEM.

A.6 Withdrawals, compliance and protocol violations:
Withdrawals: Three subjects withdrew during the protocol. One subject withdrew prior to dosing due to failure to meet eligibility requirements. Subject 206 was withdrawn after receiving regimens B and C due to a reported "elevated predose QTc". Subject 229 (completed regimens A, D, E, and F) was withdrawn at the investigator's discretion. There was an error in obtaining the laboratory samples, but 2 of the 5 periods were used for analysis.

Reviewer's Comment: For subject 206, the reported values in Table D19, page 1856, show predose absolute QT of 445 msec, QTcF of 426 msec, and QTci of 440 msec. The cited criteria for withdrawal based on QT interval is QTc>440. Based on this value, subject 206 does not meet withdrawal criteria.

Compliance: Study medication was administered under the supervision of study personnel. The oral cavity of each subject was examined following dosing to ensure that study medication was taken.
Protocol violations: 1) Protocol violations were related to performance of ECG recordings. Nine subjects had ECGs taken 1 to 11 minutes late, for 2 subjects the timing of ECGs within a sequence of 6 ECGs at one given timepoint differed from the 1 minute specified by the protocol, and 1 subject had only 5 ECGs taken at one particular timepoint. In addition, 1 subject had 2 out of 6 predose ECGs with a PR interval greater than 240 msec. These deviations were noted but were not considered sufficient reason for withdrawal, nor were they considered to substantially affect the conclusions of the study.

Reviewer's comment: This reviewer agrees that the ECG related deviations were not substantial to affect the study conclusions.

2) Three subjects received medication or nutritional supplements within 7 days of the start of dosing and 2 subjects received prohibited medication during the study. These subjects and the medications they received are summarized in Table A.3. Concomitant medications by subject 102 were taken 3 days after dosing with sildenafil 400 mg in Session 5, and did not affect ECGs recorded during Session 5 or during the following session (Session 6, moxifloxacin 400 mg was given 15 days later).

Table A.3 Medication Violations

Subject	Prohibited Medication
Prior Medications	
113	Vitamins A, C, D, E as nutritional supplement
233	Aspirin for prophylaxis Metamucil for prophylaxis
236	Aspirin for prophylaxis
Concomitant Medications	
102	Cipro for inflammation Endocet for pain MSO4 for pain Percocet for pain Phergan for nausea/vomiting Toradol for pain Ultram for pain
234	Prune juice for constipation

Source: Tables 12.5, 12.6

A.7 Pharmacokinetic and pharmacodynamic analysis:

A.7.1 Pharmacokinetic analysis:

There was an error involving switching of samples (moxifloxacin sample was assayed for vardenafil, vardenafil 10 mg sample was assayed for sildenafil) that resulted in non-quantifiable concentrations for subject 229. As a result, 57 subjects (instead of 58) were included in the pharmacokinetic analysis for vardenafil (10 mg), sildenafil (400 mg) and moxifloxacin (400 mg) while a total of 58 subjects were utilized in the pharmacokinetic analysis for vardenafil (80 mg) and sildenafil (50 mg). Table A.4 summarizes the PK analysis.

Table A.4

Parameter (units)	Vardenafil 10 mg (N=57)	Vardenafil 80 mg (N=58)	Sildenafil 50 mg (N=58)	Sildenafil 400 mg (N=57)	Moxifloxacin 400 mg (N=57)
Cmax (ng/mL)	8.83 (3.87)	106 (59)	178 (68.4)	1519 (563)	2931 (684)
Tmax[a] (hour)	1.17	1.17	1.17	1.67	1.22

[a] Median (range)

Based on the mean data, *Cmax* values for vardenafil and sildenafil increased with dose in a greater than dose proportional manner (approximately 12-fold increase in mean Cmax for an 8-fold increase in dose). The sponsor states that the Cmax values observed following single oral 10 and 80 mg vardenafil administration were consistent with those observed previously in earlier Phase I clinical trials and the reported values for both sildenafil and moxifloxacin were consistent with reported values in the literature.

Based on median values, *Tmax* occurred at approximately 1.2 hour postdose following single oral 10 and 80 mg vardenafil, 50 mg sildenafil, and 400 mg moxifloxacin administration. The time to reach maximum plasma concentration occurred later following 400 mg single oral sildenafil compared to the 80 mg vardenafil group. Approximately 61% subjects receiving 400 mg sildenafil had Tmax achieved at more than 1.0 hours postdose in comparison to 31% subjects receiving 80 mg vardenafil.

A.7.2 Pharmacodynamic analysis:

A.7.2.1 Results at 1 hour post-dose:

Change in QTcF:

Point estimates and 90% confidence intervals for change from baseline at 1 hour post-dose for QTc corrected using Fridericia's formula are provided in Table A.5. For a single dose of 80 mg of vardenafil, based on change from baseline at 1 hour post-dose, an effect greater than 10 msec on QTc as compared to placebo could not be ruled out as the upper 90% confidence interval was greater than 10 msec. A single dose of sildenafil 400 mg had a similar effect on QTcF as vardenafil 80 mg. The lower doses of vardenafil and sildenafil had effects on QTcF that were smaller than the higher doses, and were similar to the effects of moxifloxacin. (The study was not statistically powered to compare different doses and different drugs. The study was designed to compare 80 mg of vardenafil with placebo).

Table A.5 : Change from baseline in QTcF (msec) at 1 hour post-dose

Regimen	Means[1] (s.e.)	Comparison	Point Estimate[2]	90%CI
Placebo	0 (0.7)			
Primary Comparison:				
80 mg vardenafil	10 (0.7)	80 mg vardenafil Placebo	10	(8, 11)
Secondary Comparison:				
10 mg vardenafil	8 (0.7)	10 mg vardenafil Placebo	8	(6, 9)
50 mg sildenafil	7 (0.7)	50 mg sildenafil Placebo	6	(5, 8)
400 mg Sildenafil	9 (0.7)	400 mg sildenafil Placebo	9	(8, 11)
400 mg moxifloxacin	8 (0.7)	400 mg moxifloxacin Placebo	8	(6, 9)

1 represents adjusted arithmetic mean 2 represents difference between arithmetic means Note: above results are rounded to the nearest integer. Source: Study report 10929. Table 12, page 60.

Change in QTci:

After the preliminary study results were reported, the sponsor submitted the QTci analysis using individually-corrected QTc following linear regression modeling of QT and RR on data from each subject. The trends in active to placebo comparisons for QTci were similar to those observed for QTcF, with the magnitude of the differences for QTci appearing to be smaller than those for QTcF. The results are shown in Table A.6.

Table A.6 Change from Baseline in QTci (msec) at 1 hour post-dose

Regimen	Means[1] (s.e.)	Comparison	Point Estimate[2]	90% CI
Placebo	2 (0.7)			
Primary Comparison:				
80 mg vardenafil	8 (0.7)	80 mg vardenafil Placebo	6	(4, 7)
Secondary Comparison:				
10 mg vardenafil	6 (0.7)	10 mg vardenafil Placebo	4	(3, 6)
50 mg sildenafil	6 (0.7)	50 mg sildenafil Placebo	4	(2, 5)
400 mg Sildenafil	7 (0.7)	400 mg sildenafil Placebo	5	(4, 7)
400 mg moxifloxacin	9 (0.7)	400 mg moxifloxacin Placebo	7	(5, 8)

1 represents adjusted arithmetic mean 2 represents difference between arithmetic means
Note: above results are rounded to the nearest integer (accounts for apparent discrepancies between means and point estimates and asymmetry of CI). Source: Study report 10929. Table 13, page 61.

Change in QT and HR:

Point estimates and 90% confidence intervals for the change from baseline QT

and HR, 1 hour post-dose are provided in Table A.7 and Table A.8, respectively. For a single 80 mg dose of vardenafil, a slight decrease from baseline (point estimate of -2 msec, 90% CI of -4 to 0 msec) at 1 hour post-dose in the QT interval was seen compared to placebo. However, change from baseline at 1 hour post-dose in HR appeared to be greater following a single 80 mg dose of vardenafil as compared to placebo. Similar effects were observed for 10 mg of vardenafil and 50 and 400 mg of sildenafil. For a single 400 mg of moxifloxacin, change from baseline at 1 hour post-dose in the QT interval appeared to be greater than that of placebo.

Table A.7 Change from Baseline in QT (msec) at 1 hour post-dose

Regimen	Means[1] (s.e.)	Comparison	Point Estimate[2]	90% CI
Placebo	6 (1.0)			
Primary Comparison:				
80 mg vardenafil	4 (1.0)	80 mg vardenafil Placebo	-2	(-4, 0)
Secondary Comparison:				
10 mg vardenafil	4 (1.0)	10 mg vardenafil Placebo	-2	(-4, 0)
50 mg sildenafil	4 (1.0)	50 mg sildenafil Placebo	-2	(-4, 0)
400 mg Sildenafil	5 (1.0)	400 mg sildenafil Placebo	-1	(-3, 1)
400 mg moxifloxacin	10 (1.0)	400 mg moxifloxacin Placebo	3	(1, 5)

1 represents adjusted arithmetic mean 2 represents difference between arithmetic means

Note: above results are rounded to the nearest integer (accounts for apparent discrepancies between means and point estimates and asymmetry of CI). Source: Study report 10929. Table 14, page 62.

Table A.8 Change from Baseline in HR (bpm) at 1 hour post-dose

Regimen	Means[1] (s.e.)	Comparison	Point Estimate[2]	90% CI
Placebo	-3 (0.5)			
Primary Comparison:				
80 mg vardenafil	3 (0.5)	80 mg vardenafil Placebo	6	(5, 7)
Secondary Comparison:				
10 mg vardenafil	2 (0.5)	10 mg vardenafil Placebo	5	(4, 6)
50 mg sildenafil	1 (0.5)	50 mg sildenafil Placebo	4	(3, 5)
400 mg Sildenafil	2 (0.5)	400 mg sildenafil Placebo	5	(4, 6)
400 mg moxifloxacin	-1 (0.5)	400 mg moxifloxacin Placebo	2	(1, 3)

1 represents adjusted arithmetic mean 2 represents difference between arithmetic means

Note: above results are rounded to the nearest integer (accounts for apparent discrepancies between means and point estimates and asymmetry of CI). Source: Study report 10929. Table 15, page 62.

A.7.2.2 Results at Tmax:

Change in QTcF:

The change from baseline in QTcF at Tmax was similar to that of the change from baseline at 1 hour post-dose, except that the change for 400 mg sildenafil at Tmax appeared to be smaller compared to the 80 mg vardenafil dose group. (The study was not statistically powered to compare different doses and different drugs. The study was designed to compare 80 mg of vardenafil with placebo). For the 400 mg sildenafil group, approximately 20-25% of subjects reached Tmax at varying time points (range 0.5- 4.0 hours). The sponsor believes that "the Tmax, and consequently Cmax, may not have been adequately characterized for sildenafil 400 mg. For subjects in the 400 mg sildenafil group with Tmax occurrence at 4 hours, the deltas appear to be less than expected."

Table A.9 Change from baseline in QTcF (msec) at Tmax post-dose

Regimen	Comparison	Point Estimate[1]	90% CI
Primary Comparison:			
80 mg vardenafil	80 mg vardenafil Placebo	9	(8, 11)
Secondary Comparison:			
10 mg vardenafil	10 mg vardenafil Placebo	7	(5, 9)
50 mg sildenafil	50 mg sildenafil Placebo	6	(5, 8)
400 mg Sildenafil	400 mg sildenafil Placebo	6	(4, 7)
400 mg moxifloxacin	400 mg moxifloxacin Placebo	8	(7, 10)

1 represents difference between arithmetic means Source: Study report 10929. Table 16, page 63.

Change in QTci:

The trends in active to placebo comparisons for QTci at Tmax were similar to those observed for QTcF, with the magnitude of the differences for QTci appearing to be smaller than those for QTcF. (Table A.10)

Table A.10 Change from baseline in QTci (msec) at Tmax post-dose

Regimen	Comparison	Point Estimate[1]	90% CI
Primary Comparison:			
80 mg vardenafil	80 mg vardenafil Placebo	6	(5, 8)
Secondary Comparison:			
10 mg vardenafil	10 mg vardenafil Placebo	3	(2, 5)
50 mg sildenafil	50 mg sildenafil Placebo	3	(2, 5)
400 mg Sildenafil	400 mg sildenafil Placebo	5	(3, 6)
400 mg moxifloxacin	400 mg moxifloxacin Placebo	7	(6, 9)

1 represents difference between arithmetic means Source: Study report 10929. Table 17, page 63.

Change in QT and HR:

Point estimates and 90% confidence intervals for the change from baseline in QT and HR at Tmax post-dose are provided in Table A.11 and Table A.12, respectively.

Table A.11 Change from Baseline in QT (msec) at Tmax post-dose

Regimen	Comparison	Point Estimate[1]	90% CI
Primary Comparison:			
80 mg vardenafil	80 mg vardenafil Placebo	-1	(-3, 2)
Secondary Comparison:			
10 mg vardenafil	10 mg vardenafil Placebo	-3	(-5, 0)
50 mg sildenafil	50 mg sildenafil Placebo	-3	(-5, -1)
400 mg Sildenafil	400 mg sildenafil Placebo	1	(-1, 4)
400 mg moxifloxacin	400 mg moxifloxacin Placebo	4	(2, 7)

1 represents difference between arithmetic means Source: Study report 10929. Table 18, page 64.

Table A.12 Change in baseline in HR (bpm) at Tmax post-dose

Regimen	Comparison	Point Estimate[1]	90% CI
Primary Comparison:			
80 mg vardenafil	80 mg vardenafil Placebo	5	(4, 6)
Secondary Comparison:			
10 mg vardenafil	10 mg vardenafil Placebo	4	(3, 5)
50 mg sildenafil	50 mg sildenafil Placebo	4	(3, 5)
400 mg Sildenafil	400 mg sildenafil Placebo	2	(1, 3)
400 mg moxifloxacin	400 mg moxifloxacin Placebo	2	(1, 3)

1 represents difference between arithmetic means Source: Study report 10929. Table 19, page 64.

A.7.2.3 Results at Mean post-dose (the mean of all post-dose measurements):

Change in QTcF:

Point estimates and 90% confidence intervals for the change from baseline in mean of all post-dose measurements is represented as "mean post-dose QTcF" and is provided in Table A.13. For a single dose of 80 mg of vardenafil as compared to placebo, the upper bound of the 90% two-sided confidence interval at mean post-dose was less than 10 msec. Single doses of 10 mg vardenafil, and 50 mg sildenafil appeared to have similar effects on QTc prolongation as compared to each other and slightly smaller effect as compared to 80 mg vardenafil, 400 mg sildenafil, and 400 mg moxifloxacin.

Table A.13 Change from Baseline in QTcF (msec) at mean post-dose

Regimen	Means[1] (s.e.)	Comparison	Point Estimate[2]	90% CI
Placebo	0 (0.5)			
Primary Comparison:				
80 mg vardenafil	8 (0.5)	80 mg vardenafil Placebo	8	(7, 9)
Secondary Comparison:				
10 mg vardenafil	5 (0.5)	10 mg vardenafil Placebo	5	(4, 6)
50 mg sildenafil	5 (0.5)	50 mg sildenafil Placebo	4	(3, 5)
400 mg Sildenafil	7 (0.5)	400 mg sildenafil Placebo	7	(6, 8)
400 mg moxifloxacin	7 (0.5)	400 mg moxifloxacin Placebo	7	(6, 8)

1 represents adjusted arithmetic mean 2 represents difference between arithmetic means

Note: above results are rounded to the nearest integer. (accounts for apparent discrepancies between means and point estimates and asymmetry of CI) Source: Study report 10929. Table 20, page 65.

Change in QTci

Point estimates and 90% confidence intervals for the change from baseline at mean post-dose in QTci are provided in Table A.14. The magnitude of the change from baseline for QTci at mean post-dose appears to be smaller than those for QTcF.

Table A.14 Change from Baseline in QTci (msec) at mean post-dose

Regimen	Means[1] (s.e.)	Comparison	Point Estimate[2]	90% CI
Placebo	2 (0.6)			
Primary Comparison:				
80 mg vardenafil	7 (0.6)	80 mg vardenafil Placebo	5	(4, 7)
Secondary Comparison:				
10 mg vardenafil	4 (0.6)	10 mg vardenafil Placebo	3	(1, 4)
50 mg sildenafil	4 (0.6)	50 mg sildenafil Placebo	3	(2, 4)
400 mg Sildenafil	7 (0.6)	400 mg sildenafil Placebo	5	(4, 6)
400 mg moxifloxacin	8 (0.6)	400 mg moxifloxacin Placebo	7	(5, 8)

1 represents adjusted arithmetic mean

2 represents difference between arithmetic means

Note: above results are rounded to the nearest integer (accounts for apparent discrepancies between means and point estimates and asymmetry of CI). Source: Study report 10929. Table 21, page 65.

Change in QT and HR:

Point estimates and 90% confidence intervals for the change from baseline at mean post-dose in QT and HR are provided in Table A.15 and Table A.16, respectively. The results are similar to those observed at 1 hour post-dose and at Tmax.

Table A.15 Change from Baseline in QT (msec) at mean post-dose

Regimen	Means[1] (s.e.)	Comparison	Point Estimate[2]	90% CI
Placebo	5 (0.9)			
Primary Comparison:				
80 mg vardenafil	5 (0.9)	80 mg vardenafil Placebo	1	(-1, 2)
Secondary Comparison:				
10 mg vardenafil	3 (0.9)	10 mg vardenafil Placebo	-1	(-3, 0)
50 mg sildenafil	4 (0.9)	50 mg sildenafil Placebo	0	(-2, 1)
400 mg Sildenafil	6 (0.9)	400 mg sildenafil Placebo	2	(0, 4)
400 mg moxifloxacin	10 (0.9)	400 mg moxifloxacin Placebo	5	(3, 7)

1 represents adjusted arithmetic mean

2 represents difference between arithmetic means

Note: above results are rounded to the nearest integer. (accounts for apparent discrepancies between means and point estimates and asymmetry of CI) Source: Study report 10929. Table 22, page 66.

Table A.16 Change from baseline in HR (bpm) at mean post-dose

Regimen	Means[1] (s.e.)	Comparison	Point Estimate[2]	90% CI
Placebo	-2 (0.4)			
Primary Comparison:				
80 mg vardenafil	1 (0.4)	80 mg vardenafil Placebo	3	(2, 4)
Secondary Comparison:				
10 mg vardenafil	1 (0.4)	10 mg vardenafil Placebo	3	(2, 3)
50 mg sildenafil	0 (0.4)	50 mg sildenafil Placebo	2	(1, 3)
400 mg Sildenafil	0 (0.4)	400 mg sildenafil Placebo	2	(1, 3)
400 mg moxifloxacin	-1 (0.4)	400 mg moxifloxacin Placebo	1	(0, 1)

1 represents adjusted arithmetic mean

2 represents difference between arithmetic means

Note: above results are rounded to the nearest integer. (accounts for apparent discrepancies between means and point estimates and asymmetry of CI) Source: Study report 10929. Table 23, page 66.

A.7.2.4 Results at Mean maximum post-dose:

Change in QTcF:

Point estimates and 90% confidence intervals for the comparisons of interest for change from baseline at maximum QTcF are provided in Table A.17.

Table A.17 Change from Baseline in max QTcF (msec)

Regimen	Means[1] (s.e.)	Comparison	Point Estimate[2]	90% CI
Placebo	4 (0.6)			
Primary Comparison:				
80 mg vardenafil	13 (0.6)	80 mg vardenafil Placebo	9	(7, 10)
Secondary Comparison:				
10 mg vardenafil	10 (0.6)	10 mg vardenafil Placebo	6	(5, 7)
50 mg sildenafil	9 (0.6)	50 mg sildenafil Placebo	5	(4, 6)
400 mg Sildenafil	12 (0.6)	400 mg sildenafil Placebo	8	(7, 9)
400 mg moxifloxacin	13 0.6)	400 mg moxifloxacin Placebo	9	(7, 10)

1 represents adjusted arithmetic mean

2 represents difference between arithmetic means

Note: above results are rounded to the nearest integer. (accounts for apparent discrepancies between means and point estimates and asymmetry of CI) Source: Study report 10929. Table 24, page 67.

Poiht estimates and 90% confidence intervals for the change from baseline at maximum QTci are provided in Table A.18.

Table A.18 Comparisons of Interest for Change from baseline in max QTci (msec)

Regimen	Means[1] (s.e.)	Comparison	Point Estimate[2]	90% CI
Placebo	6 (0.7)			
Primary Comparison:				
80 mg vardenafil	12 (0.7)	80 mg vardenafil Placebo	6	(5, 8)
Secondary Comparison:				
10 mg vardenafil	9 (0.7)	10 mg vardenafil Placebo	4	(2, 5)
50 mg sildenafil	9 (0.7)	50 mg sildenafil Placebo	3	(2, 5)
400 mg Sildenafil	12 (0.7)	400 mg sildenafil Placebo	6	(5, 8)
400 mg moxifloxacin	14 0.7)	400 mg moxifloxacin Placebo	8	(7, 9)

1 represents adjusted arithmetic mean
2 represents difference between arithmetic means
Note: above results are rounded to the nearest integer. (accounts for apparent discrepancies between means and point estimates and asymmetry of CI) Source: Study report 10929. Table 25, page 67.

Point estimates and 90% confidence intervals for the change from baseline in QT and HR at the time that maximum QTcF and QTci occurred are provided in Table A.19 through Table A.22.

Table A.19 Change from Baseline in QT (msec) at the time of max QTcF

Regimen	Means[1] (s.e.)	Comparison	Point Estimate[2]	90% CI
Placebo	7 (1.2)			
Primary Comparison:				
80 mg vardenafil	6 (1.2)	80 mg vardenafil Placebo	-1	(-3, 1)
Secondary Comparison:				
10 mg vardenafil	5 (1.2)	10 mg vardenafil Placebo	-2	(-4, 0)
50 mg sildenafil	5 (1.2)	50 mg sildenafil Placebo	-2	(-4, 1)
400 mg Sildenafil	8 (1.2)	400 mg sildenafil Placebo	0	(-2, 3)
400 mg moxifloxacin	14 (1.2)	400 mg moxifloxacin Placebo	7	(4, 9)

1 represents adjusted arithmetic mean 2 represents difference between arithmetic means
Note: above results are rounded to the nearest integer. (accounts for apparent discrepancies between means and point estimates and asymmetry of CI) Source: Study report 10929. Table 26, page 68.

Table A.20 Change from Baseline in QT (msec) at the time of max QTci

Regimen	Means[1] (s.e.)	Comparison	Point Estimate[2]	90% CI
Placebo	8 (1.2)			
Primary Comparison:				
80 mg vardenafil	11 (1.2)	80 mg vardenafil Placebo	3	(1, 5)
Secondary Comparison:				
10 mg vardenafil	9 (1.2)	10 mg vardenafil Placebo	0	(-2, 3)
50 mg sildenafil	9 (1.2)	50 mg sildenafil Placebo	0	(-2, 2)
400 mg Sildenafil	12 (1.2)	400 mg sildenafil Placebo	4	(1, 6)
400 mg moxifloxacin	15 (1.2)	400 mg moxifloxacin Placebo	7	(5, 9)

1 represents adjusted arithmetic mean
2 represents difference between arithmetic means
Note: above results are rounded to the nearest integer. (accounts for apparent discrepancies between means and point estimates and asymmetry of CI) Source: Study report 10929. Table 27, page 68.

Table A.21 Change from Baseline in HR (bpm) at the time of max QTcF

Regimen	Means[1] (s.e.)	Comparison	Point Estimate[2]	90% CI
Placebo	-1 (0.6)			
Primary Comparison:				
80 mg vardenafil	3 (0.6)	80 mg vardenafil Placebo	5	(3, 6)
Secondary Comparison:				
10 mg vardenafil	3 (0.6)	10 mg vardenafil Placebo	4	(3, 5)
50 mg sildenafil	2 (0.6)	50 mg sildenafil Placebo	3	(2, 4)
400 mg Sildenafil	2 (0.6)	400 mg sildenafil Placebo	3	(2, 5)
400 mg moxifloxacin	-1 (0.6)	400 mg moxifloxacin Placebo	1	(0, 2)

1 represents adjusted arithmetic mean 2 represents difference between arithmetic means
Note: above results are rounded to the nearest integer. (accounts for apparent discrepancies between means and point estimates and asymmetry of CI) Source: Study report 10929. Table 28, page 68.

Table A.22 Change from Baseline in HR (bpm) at the time of max QTci

Regimen	Means[1] (s.e.)	Comparison	Point Estimate[2]	90% CI
Placebo	-2 (0.6)			
Primary Comparison:				
80 mg vardenafil	0 (0.6)	80 mg vardenafil Placebo	2	(1, 3)
Secondary Comparison:				
10 mg vardenafil	0 (0.6)	10 mg vardenafil Placebo	2	(1, 3)
50 mg sildenafil	0 (0.6)	50 mg sildenafil Placebo	2	(0, 3)
400 mg Sildenafil	0 (0.6)	400 mg sildenafil Placebo	2	(0, 3)
400 mg moxifloxacin	-1 (0.6)	400 mg moxifloxacin Placebo	0	(-1, 2)

1 represents adjusted arithmetic mean 2 represents difference between arithmetic means
Note: above results are rounded to the nearest integer. (accounts for apparent discrepancies between means and point estimates and asymmetry of CI) Source: Study report 10929. Table 29, page 69.

A.7.2.5 Outlier Analysis:

There were no uncorrected QT values > 500 msec.

a. QTcF

QTcF > 450 msec:
There were no QTcF values > 450 msec.

QTcF increase > 60 msec:
There were no *mean differences (average of 6 recordings)* greater than 60 msec for any subject or regimen.

QTcF increase > 30 msec:
There was 1 subject (#241) with a *mean difference (average of 6 recordings)* of QTcF > 30 msec following sildenafil 400mg at 1 hr post-dose.

There were 62 occurrences out of 10440 recordings of change from baseline > 30 msec. For each regimen there were 1740 total values and these 62 occurrences were seen in 20 of the 60 subjects. Out of these 62 data points, 10 were in 10 mg vardenafil group, 16 were in 80 mg vardenafil group, 10 were in 50 mg sildenafil group, 8 in 400 mg sildenafil group, 16 were in 400 mg moxifloxacin group and 2 in placebo group. Results are shown in Table A.23 and Table A.24.

Table A.23 Occurrences of Changes from Baseline Greater than 30msec in QTcF

Frequency	Regimen						
Percent	A	B	C	D	E	F	Total
QTcF < 30 msec	1730	1724	1730	1732	1724	1738	10378
	99.43	99.08	99.43	99.54	99.08	99.89	99.41
^{QTcF} ≥ 30 msec and < 60 msec	10	16	10	8	16	2	62
	0.57	0.92	0.57	0.46	0.92	0.11	0.59
Total	1740	1740	1740	1740	1740	1740	10440

Regimen A = Vardenafil 10 mg; Regimen B = Vardenafil 80 mg; Regimen C = Sildenafil 50 mg; Regimen D = Sildenafil 400 mg; Regimen E = Moxifloxacin 400 mg; Regimen F = Placebo
Source: Study 10929, table 30, page 70.

Table A.24 Number of subject-sessions with changes from baseline greater than 30 msec in QTcF (individual recordings)

Frequency	Regimen						
Percent	A	B	C	D	E	F	Total
QTcF < 30 msec	51	49	53	53	49	56	311
	14.53	13.96	15.10	15.10	13.96	15.95	89.37
QTcF ≥ 30 msec and < 60 msec	7	9	5	5	9	2	37
	1.99	2.56	1.42	1.42	2.56	0.57	10.63
Total	58	58	58	58	58	58	348

Regimen A = Vardenafil 10 mg; Regimen B = Vardenafil 80 mg; Regimen C = Sildenafil 50 mg; Regimen D = Sildenafil 400 mg; Regimen E = Moxifloxacin 400 mg; Regimen F = Placebo
Source: Study 10929, table 31, page 70.

b. QTci

QTci > 480 msec:
There were no occurrences of QTCi > 480 msec.

QTci > 450 msec:
There were 24 out of 16749 (0.14%) occurrences of QTci greater than 450 msec (but less than or equal to 480 msec). Out of these 24 data points, 3 were in 80 mg vardenafil group (range 450-461 msec), 19 were in 50 mg sildenafil group (range 450-461 msec) and 2 were in 400 mg moxifloxacin group (range 451-458 msec). These 24 occurrences were seen in 3 out of 58 subjects.

QTci increase > 60 msec:
There were no *mean differences (average of 6 recordings)* greater than 60 msec at 1 hr post-dose.

QTci increase > 30 msec:
There were no *mean differences (average of 6 recordings)* greater than 30 msec at 1 hr post-dose. Out of 10440 recordings, there were 30 occurrences (0.29%) of changes from baseline greater than 30 msec. For each regimen there were 1740 total values and these 30 occurrences were seen in 20 of the 58 subjects (see Table A.25 and Table A.26). Out of these 30 data points, 2 were in 10 mg vardenafil group, 4 were in 80 mg vardenafil group, 1 was in 50 mg sildenafil group, 4 in 400 mg sildenafil group, 18 were in 400 mg moxifloxacin group and 1 in placebo group.

Table A.25 Occurrences of changes from baseline greater than 30 msec in QTCi

Frequency	Regimen						
Percent	A	B	C	D	E	F	Total
QTci < 30 msec	1738 99.89	1736 99.77	1739 99.94	1736 99.77	1722 98.97	1739 99.94	10410 99.71
QTci ≥ 30 msec and < 60 msec	2 0.11	4 0.23	1 0.06	4 0.23	18 1.03	1 0.06	30 0.29
Total	1740	1740	1740	1740	1740	1740	10440

Regimen A = Vardenafil 10 mg; Regimen B = Vardenafil 80 mg; Regimen C = Sildenafil 50 mg; Regimen D = Sildenafil 400 mg; Regimen E = Moxifloxacin 400 mg; Regimen F = Placebo Source: Study 10929, table 32, page 71.

Table A.26 Number of subject-sessions with changes from baseline greater than 30 msec in QTci (individual recordings)

Frequency	Regimen						
Percent	A	B	C	D	E	F	Total
QTci < 30 msec	56 96.55	54 93.10	57 98.28	56 96.55	48 82.76	57 98.28	328 94.25
QTci ≥ 30msec and < 60 msec	2 3.45	4 6.90	1 1.72	2 3.45	10 17.24	1 1.72	20 5.75
Total	58	58	58	58	58	58	348

Regimen A = Vardenafil 10 mg; Regimen B = Vardenafil 80 mg; Regimen C = Sildenafil 50 mg; Regimen D = Sildenafil 400 mg; Regimen E = Moxifloxacin 400 mg; Regimen F = Placebo source: Study 10929, table 33, page 71.

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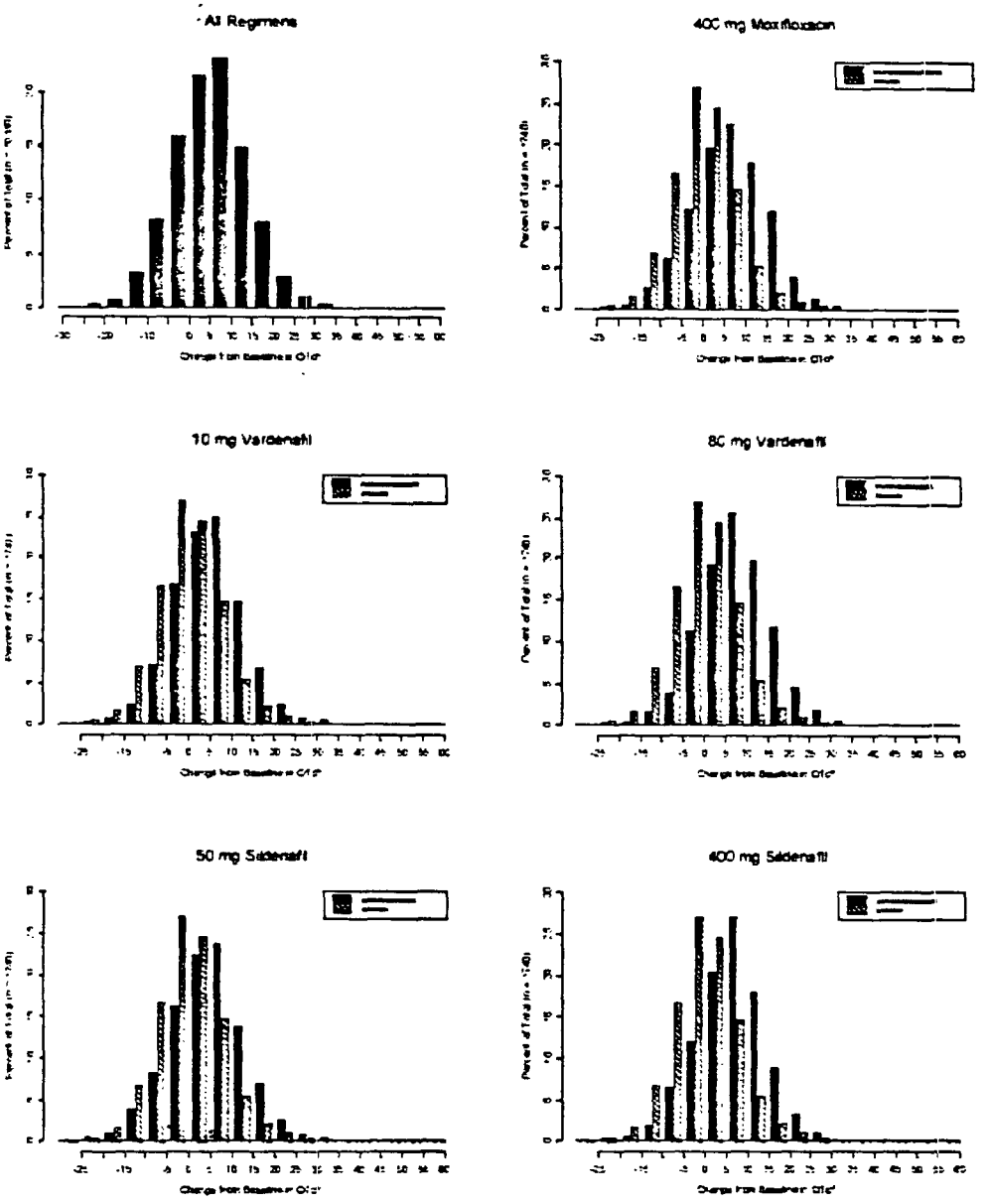
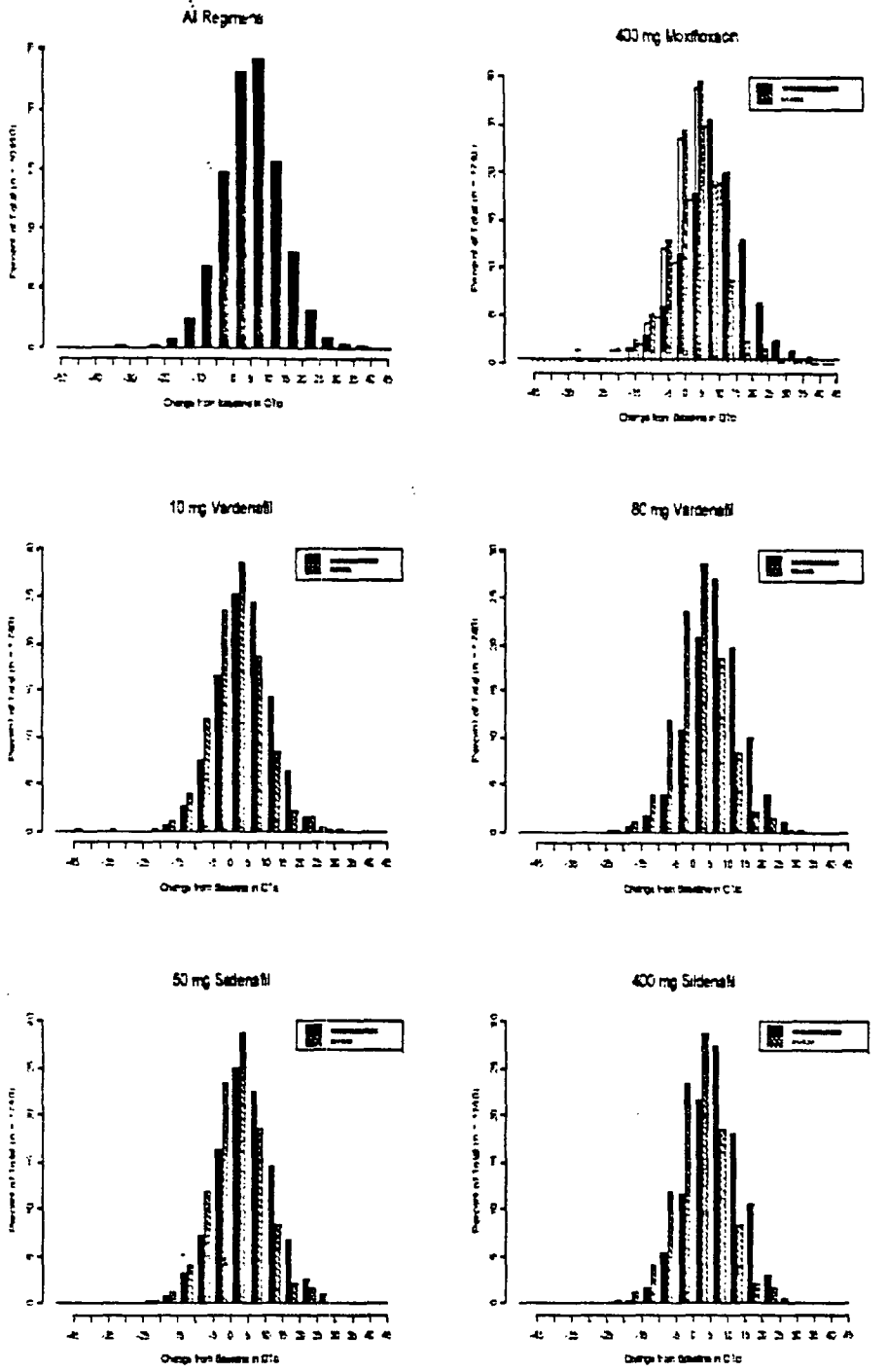
ON ORIGINAL

Figure A.1 Histograms of individual changes from baseline for QTcF (msec)



Source: Study 10929, Appendix D, Figure D1.

Figure A.2 Histograms of individual changes from baseline for QTci (msec)



Source: Study 10929, Appendix D, Figure D2.

A.8 Safety analysis:

A.8.1 Extent of exposure: 59 subjects were exposed to the study medication. 57 subjects completed the full course. Subject 206 completed regimens B (vardenafil 80 mg) and C

(sildenafil 50 mg). Subject 229 completed regimens A (vardenafil 10 mg), D (sildenafil 400mg), E (moxifloxacin 400 mg), and F (placebo).

A.8.2 Serious adverse events: There were no deaths or serious adverse events reported during the study.

A.8.3 Discontinuation due to adverse events: No subjects discontinued the study due to an adverse event.

A.8.4 Frequent adverse events:

There were a total of 186 adverse events reported across the study regimens. The most common AE was headache, followed by flushing and abnormal vision. Subjects reported the highest number of AEs during Regimen B (vardenafil 80 mg) and Regimen D (sildenafil 400 mg), and the lowest number during Regimen F (placebo). Adverse events reported by 2 or more subjects are summarized in Table A.27. Abnormal vision and photophobia were reported only in the high dose vardenafil and sildenafil regimens. Vision abnormalities included hazy vision (2 subjects), blurred vision (6 subjects), perception of increased visual acuity (1 subject), and unspecified visual disturbance (8 subjects). All cases were mild and considered related to study medication, and resolved without intervention.

Back pain or myalgia was reported in seven subjects, five subjects in regimen B (80 mg vardenafil) and 2 subjects in regimen D (400 mg sildenafil). Onset of pain following medication administration ranged from 30 minutes to 48 hours. All cases were mild and resolved. Acetominophen was required for only 1 subject (#239).

Table A.27 Adverse events reported by 2 or more subjects

Adverse Event	Regimen					
(Preferred Term)	A	B	C	D	E	F
Headache	8	23	14	12	4	4
Flushing	1	3	4	8	1	
Vision abnormal		4		13		1
Rhinitis		6	1	4	1	
Dizziness		1	1	5		
Back pain		5		2		
Dyspepsia		3	1	1		
Myalgia	1			3		
Nausea		1	1	1	1	
Diarrhea		1		1	1	
Lacrimation abnormal		1	1	1		
Abdominal pain	1	1		1		
Alopecia	1		1			
Constipation		1	1			
Fatigue			2			
Hot Flushes		1		1		
Paresthesia			1		1	
Photophobia		2				
Sweating increased			1		1	
Total number of AEs	**16**	**60**	**31**	**62**	**11**	**6**
Number of subjects with AEs	**12**	**35**	**21**	**27**	**6**	**5**
Number of subjects exposed	**58**	**58**	**58**	**58**	**58**	**58**

Regimen A = Vardenafil 10 mg; Regimen B = Vardenafil 80 mg; Regimen C = Sildenafil 50 mg; Regimen D = Sildenafil 400 mg; Regimen E = Moxifloxacin 400 mg; Regimen F = Placebo
Source: Table 12.8

Table A. 28 Adverse event: Back pain[a]

Regimen	Subject	Onset after medication	Duration	Treatment
B	208	48 hours	1 day	—-
B	215	13 hours	1 week	—-
B	220	5 hours	6 days	—-
B	235	12 hours	2 days	—-
B	241	5 hours	4 days	—-
D	239	30 min	3 days	Acetominophen
D	248	24 hours	2 days	—-

[a]All symptoms were described as contanst and mild.
B= vardenafil 80 mg D= sildenfil 400 mg

A.8.5 Clinically significant events: Vital signs:

Post-dose vital signs that exceeded protocol-defined values of clinical concern were reported for 10 subjects totaling 13 episodes, 3 subjects following administration of vardenafil 10 mg, 3 subjects following administration of vardenafil 80 mg, 3 subjects following administration of sildenafil 50 mg, 1 subject following administration of sildenafil 400 mg, and 3 subjects following moxifloxacin/placebo. The SBP change ranged from a drop of 73 mmHg to a rise of 36 mmHg. The DBP change ranged from a drop of 27 mmHg to a rise of 24 mmHg. The observed changes were described as isolated, asymptomatic occurrences.

Table A.29 Vital signs: Outliers

Subject	Regimen	Parameter	Baseline Value	Time of Assessment (D:H:M)	Value of Concern
113	A	DBP (mmHg)	86	1:1:0	61
229	A	DBP (mmHg)	78	1:0:30	57
208	A	SBP (mmHg)	158	1:1:30	126
	B	SBP (mmHg)	127	1:0:30 to 1:4:0	81-89
226	B	SBP (mmHg)	145	1:1:0	114
102	B	DBP (mmHg)	88	1:1:0	66
109	C	SBP (mmHg)	112	1:4:0	148
204	C	SBP (mmHg)	182	1:0:30 to 1:4:0	109-127
	C	DBP (mmHg)	92	1:2:30, 1:4:0	65, 68
	D	SBP (mmHg)	174	1:0:30 to 1:4:0	112-133
202	E	DBP (mmHg)	74	1:2:30	49
210	E	DBP (mmHg)	71	1:0:30	95
228	F	SBP (mmHg)	115	1:4:0	152

Regimen A = Vardenafil 10 mg; Regimen B = Vardenafil 80 mg; Regimen C = Sildenafil 50 mg;
Regimen D = Sildenafil 400 mg; Regimen E = Moxifloxacin 400 mg; Regimen F = Placebo
Source: Table 12.9

A.8.6 Changes in laboratory values:

Table A.30 Laboratory values: Outliers

Subject	Treatment	Parameter	Reference Range	Baseline Value	Time of Assessment (D:H)	Value of Concern
109	B	AST	6-34 UIU/L	15	1:24:0	71
	B	creatine kinase*	0-235 IU/L	70	1:24:0	1281, 476
231	B	glucose	72-116 mg/dl	116	1:24:0	129, 127
113	E	glucose	72-116 mg/dl	117	1:24:0 repeat	133

Regimen A = Vardenafil 10 mg; Regimen B = Vardenafil 80 mg; Regimen C = Sildenafil 50 mg;
Regimen D = Sildenafil 400 mg; Regimen E = Moxifloxacin 400 mg; Regimen F = Placebo
Source: Table B1, Appendix B * elevation was associated with lifting furniture

Post-dose laboratory values that exceeded protocol-defined values of clinical concern were reported for 4 subjects, as shown in Table A.30. Subject 109's increase in creatine kinase levels was thought to be related to physical exertion (moving heavy furniture) the preceding week.

A.9 Statistical analysis: Refer to the statistical review.
The primary endpoint, change from baseline at 1 hour post-dose for QTc, was analyzed by analysis of covariance (ANCOVA) fitting terms for sequence, subject-within-sequence, period and regimen and fitting baseline QTc as a covariate. Point estimates and 90% confidence intervals were constructed for the difference, active - placebo, for each dose of vardenafil, sildenafil and moxifloxacin using the residual variance. A greater than 10 msec effect was to be ruled out for the 80 mg dose of vardenafil when the upper 90% confidence interval for the difference between single 80 mg oral dose of vardenafil and placebo was less than 10 msec. Ninety percent (90%) CI for all other effects of interest were used to provide a range of plausible effects. Secondary endpoints for QT and HR, change from baseline at 1 hour post-dose were analyzed in a similar manner.

The exploratory endpoints, maximum QTc and QTc mean post-dose, were analyzed in a similar manner as the primary endpoint, with appropriate baseline in the model. Point estimates and 90% confidence intervals were constructed for the difference, active - placebo, for each dose of vardenafil, sildenafil and moxifloxacin using the residual variance.

Target sample size:
A sufficient number of subjects (approximately 72 subjects) were to be enrolled to ensure 54 subjects complete the study. The sample size was derived in order to address the primary objective for QTc at 1 hour post-dose. Results for all other secondary objectives and secondary endpoints were to be expressed as point and interval estimates for the effects of interest.

Within-subject variability (expressed as standard deviation) of change from baseline in QTc at 1 hour post-dose was estimated to be 11.6 msec [data on file with Bayer]. As six replicate measurements of ECGs were to be performed at each time point, it was expected that the variability will be between 11.6 and $11.6/\sqrt{6}$ (=6.7). As such, sample size calculations were based on the average of these two variables, 9.5 msec.

A.10 Reviewer's assessment
In the opinion of this reviewer, this study was adequately designed. The primary endpoint (QTcF showed a 10 msec (90% CI: 8,11) increase for vardenafil 80 mg compared to placebo. The magnitude of the QTci increase was less [(mean8 msec) 90% CI 4,7]. The significance of these finding is discussed in the Executive Summary section of this review.

Appendix B: "A randomized, double blind, placebo-controlled, cross-over study to evaluate the potentiation of the blood pressure lowering effect of sublingual nitroglycerin in combination with the PDE-5 inhibitor, vardenafil (20 mg), in healthy male subjects" (Trial 10720). Trial start date: August 15, 2002. Trial end date: December 6, 2002. Principal investigator: Miguel Zinny, MD. Study center: ProMedica Clinical Research Center, Inc., Brighton, MA.

Rationale for the study: A previously submitted study (100304) used vardenafil 10 mg in combination with 0.4 mg NTG and found no additive effect on blood pressure. Since 20 mg is the maximum to-be-marketed dose, this study was undertaken.

B.1 Objectives

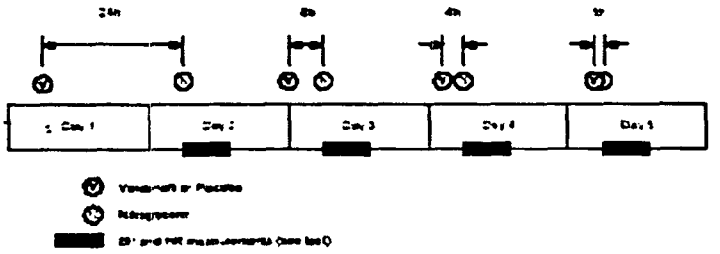
Evaluation of the pharmacodynamic (BP and HR) interaction between vardenafil (20 mg) and the standard dose of 0.4 mg sublingual NTG with separation of the two drugs by 24 hours, 8 hours, 4 hours and 1 hour.

B.2 Design and conduct summary

This was a Phase I, randomized, placebo-controlled, multiple-dose, two-period crossover study of healthy subjects. Each period was 5 consecutive days in duration. During each period, drug or placebo was administered on four evaluation days, the morning of days 1, 3, 4, and 5. NTG was administered on days 2 through 5. On each occasion, NTG was given after the study drug (see Figure B.1). NTG response was evaluated over 6 hours. On the first evaluation day, NTG was given 24 hours after study drug. On the 2nd, 3rd and 4th evaluation days, the interval between study drug and NTG was reduced to 8, 4, and 1 hour, respectively. The second period of the crossover was identical except that vardenafil was substituted for placebo or vice versa based on randomization.

All doses of study drug and NTG were taken at least 4 hours after a meal. NTG administration took place at 8:00 AM on each of the study days to minimize the influence of diurnal rhythm on the blood pressure and heart rate observations.

Figure B.1 Relationship of NTG and study drug administration



Pharmacodynamics: Blood pressure and heart rate were measured using an automated syphygmomanometer [redacted] in the seated position, followed by standing measurements after 2 minutes. The blood pressure response to NTG was assessed using a series of seated and standing measurements starting 15-20 minutes before the NTG dose and every 2 minutes following the NTG dose up to 30 minutes and then every ten minutes to the 1 hour time-

point. Following this, readings were obtained 1.5, 2, 3, 4, 5 and 6 hours after NTG dosing. Manual readings were obtained but were not included in the statistical analysis.

Pharmacokinetics: Blood samples for vardenafil were drawn at 30, 60, 90, 120, and 180 minutes after the dose of the study drug on Day 1 of both periods (Visits 1 and 2). Blood samples were also drawn approximately 60 minutes after each dose of NTG on Days 2, 3, 4, and 5 at Visits 1 and 2.

B.3 Study population

Eighteen (18) healthy male subjects (age 40-69) were included in the study. Mean age was 53 years.

Table B.1 Demographic data

Age - mean in yrs, (SD), range	52.8 (10.9) 40-69
Race	
Caucasian n (%)	12 (67%)
Black n (%)	5 (28%)
Asian n (%)	1 (6%)
Weight- mean in kg, (SD), range	85.6 (10.1) 68-106

Source: Table 11-1, study report, p. 2-18.

B.4 Inclusion and exclusion criteria

B.4.1 Inclusion criteria

- Healthy male subjects, or male subjects with erectile dysfunction, aged 40 to 70 years able to give written informed consent
- Subjects must test negative for drugs of abuse at the screening visit

Reviewer's comment: The inclusion criteria are acceptable. However, the number of men (healthy vs erectile dysfunction) is not included in the report. Theoretically, those with erectile dysfunction also have systemic vascular disease and may have a more profound hemodynamic response to study drug and NTG.

B.4.2 Exclusion criteria

- Failure of a major organ system
- Medical disorder, with the exception of erectile dysfunction, that would impair the subject's ability to complete this study (in the opinion of the investigator and the sponsor), eg, history of blood coagulation disorders
- Body mass index exceeding 37
- Symptomatic postural hypotension (eg, dizziness, lightheadedness)
- Supine systolic blood pressure must be between 100 and 150 mmHg inclusive
- Supine diastolic blood pressure must be between 60 and 95 mmHg inclusive
- Sinus bradycardia (<45 bpm) or resting pulse rate greater than 110 bpm
- Malignancy (other than squamous or basal cell carcinoma in situ) not considered cured according to the criteria of the American Cancer Society
- Acute or significant psychiatric or mental illness
- Prior history of epilepsy or other seizure disorders
- Known drug hypersensitivity, especially to PDE-5 inhibitors

• Concurrent use of anti-arrhythmia medication, anti-anginal medication, and anti-hypertensive medication
• Drugs known to interfere with the cytochrome P-450 enzyme system, specifically, corticosteroids, azole anti-mycotics (except fluconazole), macrolides (except azithromycin), phenytoin, nefazodone, rifampin, ritonavir, indinavir, androgens, and immunosuppressants
• Use of Viagra® (sildenafil) within 48 hours of any dosing (study drug or NTG) day
• Grapefruit juice or products containing grapefruit juice within 24 hours before the first dose of study drug (Day 1 of Visits 1 and 2)
• AST, ALT, LDH >1.5 times the upper limit of normal at screening and optional follow-up
• Creatine kinase (CK) levels > 3 times the upper limit of normal at screening
• Hematocrit value <32% at screening
• Serum creatinine >2.0 mg/dl at screening
• Other abnormal laboratory parameters determined to be clinically significant (in the opinion of the Investigator and the Sponsor). Laboratory values, which were slightly outside the normal ranges, were allowable; however, these out-of-range values had to be evaluated in consultation with the Sponsor
• Donation of blood within 30 days of Visit 1
• Recent participation in an investigational drug study during which active medication was given within 30 days of Visit 1
• History of drug or alcohol abuse in the 3 years prior to screening for this trial, or current intake of >14 standard alcoholic drinks per week defined as 1 oz liquor, 12 oz beer, or 6 oz wine

Reviewer's comment: The exclusion criteria are acceptable. It is noted that patients with postural hypotension or low blood pressure have been excluded.

B.5 Primary and Secondary Endpoints

B.5.1 Pharmacodynamic Evaluation:
Primary: The maximum decrease in seated SBP following the NTG dose.
Secondary: (1) maximum decrease in the seated DBP following the NTG dose; (2) maximum increase in the seated HR following the NTG dose; (3) mean change in seated SBP, DBP, and HR following the NTG dose (calculated from the area under the effect curve for BP or HR and dividing it by the period of interest). Analyses were performed for the periods 0-2 hr and 0-6 hr following NTG administration.

B.5.2 Pharmacokinetic: Vardenafil concentration was measured 1 h after administration of NTG. The tmax of vardenafil is 20-75 minutes and is predominately metabolized by CYP 3A4. The t ½ of the parent drug is 3-5 hours, and an active metabolife has a similar half-life.

B.5.3 Safety:
Standard reporting of adverse events

B.6 Withdrawals, Compliance and Protocol violations

B.6.1 Withdrawals: There were no withdrawals.

B.6.2 Compliance: Doses were supplied to the subjects under supervision.

B.6.3 Protocol violations:
(1) The protocol states an interest in the period up to 6 hours following administration of NTG. The sponsor states the data collected showed BP and HR variables returning to baseline around 60-120 minutes after NTG with maximal changes occurring between 0 and 120 minutes. As a result, an additional analysis was performed for the period 0 to 2 hours. The sponsor suggests that this analysis "yielded comparable estimates of treatment effects".
(2) Dosing on Day 5 of period 1 (NTG 1 h following vardenafil) was withheld in one subject (10720-001-1011) due to hypotension on 2 previous days.

Reviewer's Comments: (1) Based on the data presented, maximal changes in BP and HR did occur between 0 and 2 hours. (2) Withholding one dose in one subject (10720-001-1011) in period 5 may cause an underestimation of the day 5 effect of vardenafil.

B.7 Pharmacodynamic analysis

B.7.1 Blood pressure response to NTG (mean data):
The mean maximal reduction in blood pressure associated with NTG was 17 to 22 mmHg (systolic) and 18 to 20 mmHg (diastolic) with an increase of 12 to16 bpm in heart rate (see Table B.2)

Table B.2 Mean maximal change in BP and HR following NTG administration and placebo-change measured from baseline over period 0-6 hours

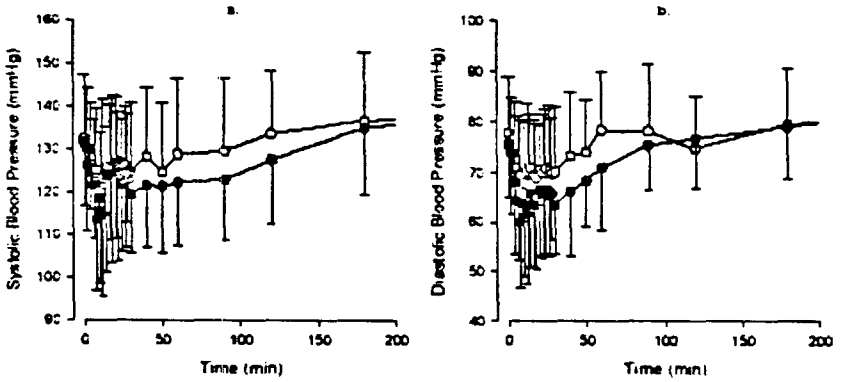
	LS Mean (n=18)		
	Systolic BP mmHg	Diastolic BP mmHg	Heart Rate Bpm
Day 2	-22.1	-18.4	15.9
Day 3	-22.1	-19.9	12.0
Day 4	-18.8	-18.1	14.6
Day 5	-16.9	-19.4	14.4

Source: Table 11-2, study report, p. 2-20.

Reviewer's comment: Maximal decrease in SBP occurred on days 2 and 3.

The mean systolic and diastolic blood pressure response to NTG on day 5 (comparing placebo with vardenafil) is shown in Figure B.2. The sponsor presents data up to 200 minutes (or 3 hours) since "it was usually the case that the maximum change from baseline occurred within the period 0-120 minutes following NTG dosing", (Table 14.2/3.3 is referenced – not shown).

Figure B.2 Mean (SD) BP on Day 5 (1 hour separation of NTG and vardenafil dosing; time=0 is dosing with NTG) n=17 to18. Source Figure 11-1, study report, p. 2-19.

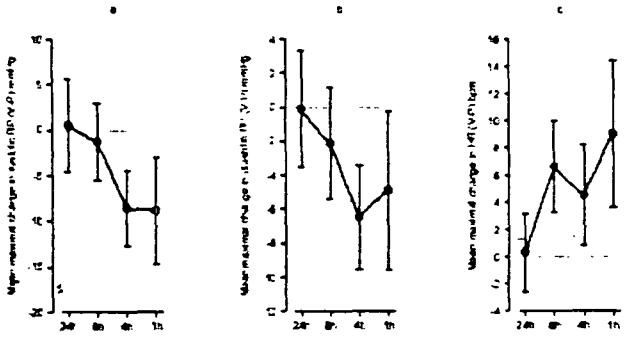


Reviewer's comment: (1)There is an observable decrease in SBP and DBP when vardenafil 20 mg is added to NTG. (2) The figure above portrays changes on day 5. The mean maximal change data table for NTG (Table B.2) shows a maximum decrease in SBP on days 2 and 3.

B.7.2 Blood pressure and heart rate- analysis of variance

Figure B.3 shows the mean maximal change (placebo-subtracted) in blood pressure and heart rate of vardenafil taken in combination with vardenafil 20 mg at differing intervals on days 2 through 5 .

Figure B.3 Point estimates of a) SBP, b) DBP, and c) HR treatment effects of pre-dosing with vardenafil with 90% CI (0-2 hr data)



Source: Figure 11-2, study report p. 2-20.

Twenty-four hours of separation of the doses of vardenafil and NTG results in NTG effects that are similar to NTG alone. Dosing with vardenafil 20 mg, 8 hours prior to NTG resulted in a significant effect on HR and small effects on blood pressure. The effect of vardenafil 20 mg, 4 or 1 hour prior to NTG produced a mean additional reduction of about 9 mmHg on systolic BP, about 6 mmHg on diastolic BP and 5 to 9

bpm increase on HR; these effects were statistically significant as indicated by the exclusion of zero from the confidence interval analysis. See Table B.3.

Table B.3 Summary of statistical analysis (ANCOVA) for BP and HR day 5

Variable	Treatment	LS mean	n	Point est.	Lower 90% CI	Upper 90% CI	P-value
Systolic BP Mean max change in 2 hr (mmHg)	Placebo	-16.78	18	-8.87	-14.95	-2.79	0.0223
	Vardenafil 20 mg	-25.65	17				
Systolic BP Mean* change over 2 hr (mmHg)	Placebo	-2.03	18	-4.57	-7.46	-1.69	0.0143
	Vardenafil 20 mg	-6.6	17				
Diastolic BP Mean max change in 2 hr (mmHg)	Placebo	-18.91	18	-5.43	-10.32	-0.54	0.0709
	Vardenafil 20 mg	-24.34	17				
Diastolic BP Mean* change over 2 hr (mmHg)	Placebo	-3.13	18	-3.4	-5.98	-0.81	0.0363
	Vardenafil 20 mg	-6.52	17				
HR Mean max change in 2 hr (bpm)	Placebo	12.67	18	6.63	1.46	11.79	0.0403
	Vardenafil 20 mg	19.3	17				
HR Mean* change over 2 hr (bpm)	Placebo	-0.85	18	1.6	-0.5	3.71	0.2009
	Vardenafil 20 mg	0.75	17				

*Derived from area under effect curve
Source: Table 11-3, study report, p. 2-22.

B.7.3 Blood pressure- categorical analysis

The pre-determined "response rate" categories of 1) drop in SBP of 25 mmHg; 2) drop in DBP of 20 mmHg; 3) absolute systolic value of 90 mmHg; or 4) absolute diastolic value of 50 mm Hg were used for this analysis. Table B.4.

Table B.4 Proportion of subjects (%) meeting response rate categories in the period 0-6 hrs after NTG

	Day 2 24 h separation	Day 3 8 h separation	Day 4 4 h separation	Day 5 1 h separation
Systolic				
delta 25 mmHg				
Vardenafil 20 mg	33	39	56	35
Placebo	17	28	22	22
absolute <90 mmHg				
Vardenafil 20 mg	6	6	28	18
Placebo	17	0	6	6
Diastolic				
delta 20 mmHg				
Vardenafil 20 mg	33	61	67	71
Placebo	33	56	39	44
absolute <50 mmHg				
Vardenafil 20 mg	22	33	44	29
Placebo	22	17	17	28

n=17-18
Source: Table 11-4, study report, p. 2-23

In general, the proportion of subjects experiencing specified changes in blood pressure from baseline (systolic and diastolic) was greater following vardenafil treatment (than placebo). Additionally, there is some evidence of a response to vardenafil concentration

as reflected in a trend for a higher proportion of affected subjects as the separation of vardenafil and NTG dosing is reduced.

B.8 Pharmacokinetic analysis (Please refer to Clinical Pharmacy Review)
A limited plasma concentration profile (samples at 0 [pre-dose], 0.5, 1, 1.5, 2 and 3 h) was performed on Day 1. Vardenafil concentrations at these time-points were consistent with those observed in other studies. Additionally, samples were taken 1 h after NTG dosing on Days 2 through 5 of the study. Considerable between-subject variability exists for vardenafil concentrations and is reflected in the overlap of the 9 hr and 2 hr data.

Examination of the relationship between vardenafil concentration and the maximal change in blood pressure revealed a trend towards a concentration response relationship

B.9 Safety analysis

B.9.1 Extent of exposure: All 18 subjects participated in Days 1 through 4 of vardenafil and Days 1 through 5 of placebo. One subject did not receive vardenafil on Day 5 of that period due to hypotensive response on 2 previous days (patient #1011).

B.9.2 Adverse events
Table B.5 lists all adverse events.

Table B. 5 All adverse events

Adverse Event	Placebo (N=18)	Vardenafil (N=18)
Any event	4 (22%)	9 (50%)
Dizziness	2 (1%)	5 (28%)
Headache	1 (6%)	1 (6%)
Hypotension	1 (6%)	3 (17%)
Sweating increased	0 (0%)	1 (6%)
Contusion	0 (0%)	1 (6%)
Nausea	0 (0%)	1 (6%)
Urinary tract infection	0 (0%)	1 (6%)
Elevated CK	1 (6%)	1 (6%)
Hematuria	1 (6%)	0 (0%)

Source: Table 14.3.1/1, study report, p. 2-175.

Adverse events were more common following vardenafil (50% reported at least one AE) than placebo (22%). Dizziness and hypotension were more common following vardenafil than placebo (28% vs 11% and 17% vs 6%), respectively. There was a tendency for these adverse events to be associated with 4 or 1 hour dose separation (day 4 or day 5) of vardenafil administration and NTG dosing, reference Table 14.3.1/3 (not shown).

B.9.3 Deaths: There were no deaths.

B.9.4 Serious adverse events:
Following completion of the study, the Department of Global Drug Safety (GDS) requested that systolic blood pressure <85 mmHg with associated symptoms be reported

as a Serious Adverse Event (SAE). Three subjects fulfilled these criteria. Additionally, one subject had hematuria after the follow-up period defined in the protocol. These SAEs are listed in Table B.6 and narratives follow.

Table B.6 Serious adverse events

Patient #	Age	Event
1003	43	symptomatic hypotension, BP 79/41 HR 6, lightheadedness
1011	67	symptomatic hypotension, BP 79/46 HR 90, lightheadedness/sweating
1027	66	gross hematuria
1038	66	symptomatic hypotension, BP 73/38 HR 70, dizziness

Source: Amended from table on p. 2-183

Narratives

Patient 1003: A 43 year-old male experienced lightheadedness with symptomatic hypotension on Day 2 of Period 1 (Placebo period). Placebo was given on Day 1 at 8 AM. Sublingual Nitroglycerin (0.4 mg) was given twenty-four hours later. His seated BP prior to NTG was 129/81, HR 69. Ten minutes after this dose, seated BP was 79/41 with HR of 60. He was placed in the supine position where his BP was 106/60, HR 66. The lightheadedness resolved after seven minutes in the supine position. Eight minutes after this event his seated BP was 120/72, HR 72. During the vardenafil period, he experienced a BP of 89/43 (HR not given) on Day 4 eight minutes after NTG administration. Day 5 was uneventful.

Reviewer's comment: Actual BP for Day 5 was not given but line listings show Day 5 maximum decrease in seated SBP of –17.5 (compared to –43.8 on Day 4).

Patient #1011: A 67 year-old male experienced lightheadedness, sweating and symptomatic hypotension on Day 3 of period 1 [Vardenafil 20 mg]. On Day 3 dosing, Vardenafil 20 mg was given at 12:01 AM and NTG at 8:00 AM. Prior to NTG dosing, his seated BP was 116/67, HR 74. Four minutes after dosing, his seated BP was 77/38, HR 90. He was placed supine for 22 minutes. His lowest supine BP during this time was 79/46, HR 65. Thirty minutes post dose seated BP was 103/65, HR 75. ECG showed no change from baseline. On Day 4, his BP dropped to 75/43 but was asymptomatic. The investigator held the patient's vardenafil dose on Day 5.

Patient #1027: A 66 year old male reported blood in his urine on November 11, 2002, (ten days after his last in-clinic study day and 24 days after the last dose of vardenafil). He reported taking Viagra on November 10, 2002, prior to having sexual relations that date. On the morning of November 11, 2002, he reported he had bright red blood in his urine. Blood in urine persisted but turned to a pinkish color by November 18, 2002. Subject denied any dysuria, urinary frequency, or back/pelvic pain. He was seen by a urologist at [redacted] on November 28, 2002, at which time an abdominal and pelvic ultrasound were done. The ultrasound reports "simple left renal cyst." The prostate measured at least 5x6 cm. Clinic urine evaluation on November 1, 2002 was negative for blood in urine (final scheduled laboratory testing). An additional report dated November 8, 2002, showed trace blood in urine (source of report unknown).

Reviewer's comment: Hemoglobin value was not found in accessory tables.

Patient #1038: A 66 year-old male had symptomatic hypotension with dizziness on Days 4 and 5 of Period 2 (vardenafil 20 mg). On Day 4, subject was dosed with vardenafil 20 mg at 4:06 AM and NTG four hours later. Seated BP pre-dose NTG was 126/78, HR 81. Six minutes after the NTG dose, his seated BP was 89/40, HR 92. He complained of dizziness one minute later (8:13 AM). He was placed supine at 8:14 AM. At 8:15 AM he "felt better". He remained supine until 8:31 AM, when he resumed the seated position. His lowest BP while supine was 73/38, HR 70. When he returned to the seated position, his BP was 108/69, HR 79, and he was asymptomatic. ECG after this episode showed no changes from baseline. On day 5 of Period 2, subject was dosed with Vardenafil 20 mg at 7:06 AM and NTG one hour later. Seated BP prior to NTG dosing was 100/65, HR 86. Six minutes post NTG dosing subject complained of dizziness accompanied by symptomatic hypotension. He was placed supine and his BP was 88/50, HR 76. He remained supine for 20 minutes and his lowest BP during this time was 97/57, HR 75. When he returned to the seated position, his BP was 113/60, HR 82. ECG after episode showed no ischemic changes.

Reviewer's comment: Two of the 3 hypotension adverse events (#1011, #1038) showed a temporal relationship to study drug intake and appear causal. The hypotension noted for patient 1003 appears NTG-related. The case of hematuria appears unrelated to study drug.

B.9.5 Laboratory outliers

Examination of this listing shows sporadic abnormalities (particularly evident for creatine kinase, cholesterol and triglycerides); however, the temporal relationship between these findings and dosing does not indicate that they are likely to be drug related.

Reviewer's comment: The line listings for laboratory abnormalities have been reviewed and I agree with the sponsor's assessment.

B.10 Statisical analysis

Blood pressure and heart rate data were analyzed using analysis of covariance (ANCOVA), with terms for sequence, subject within sequence, period, and treatment with baseline as a covariate. Change from baseline was determined for each variable with the baseline established from the mean of all BP readings within 60 minutes prior to the NTG dose. The treatment comparison (vardenafil vs placebo) was of primary interest. These analyses were performed under each of the four conditions being assessed: NTG given 24 hours, 8 hours, 4 hours and 1 hour after a vardenafil/placebo dose (Days 2, 3, 4 and 5 of the study, respectively). The BP and HR response to NTG was assessed using maximal change from baseline and mean change from baseline (calculated from area under the effect curve for BP and HR). Analyses were performed for the periods 0-2 hr and 0-6 hr following NTG administration.

Additionally, the BP "response rate" was determined using the following thresholds:

change in sitting systolic BP of 25 mmHg; change in sitting diastolic BP of 20 mmHg; absolute value of sitting systolic BP <90 mmHg; absolute value of sitting diastolic BP <50 mmHg. These analyses were performed for the period 0 to 6 hr following NTG administration.

The frequency-of-response was tabulated by treatment group and McNemar's test for comparisons of rates was performed.

The limit of quantitation (LOQ) for BAY 38-9456 and BAY 44-5576 plasma concentration was — µg/l. For the purposes of analysis, summary, and graphical display of mean plasma concentrations, values below LOQ were replaced by — µg/l (ie, one-half of the limits). However, means and standard deviations of plasma concentrations at each sampling time point were calculated only when at least 2/3 of the data were above the LOQ. The median was calculated when at least half the data were above the LOQ. The maximum value was calculated when at least one value was above the LOQ.

B.11 Determination of sample size

In the recently completed Bayer interaction study of 10 mg vardenafil and NTG (study 10304), a standard deviation (SD) of the differences was found to be 9 mmHg. Therefore, 18 subjects would allow greater than 90% power to detect a difference of 10 mmHg at the 0.05 level of significance.

B.12 Sponsor's conclusions

(1) NTG caused an abrupt short-lived decrease in blood pressure and a compensatory increase in heart rate.
(2) Twenty-four hour separation of the doses of vardenafil and NTG results in NTG effects that are similar to NTG alone.
(3) Dosing with vardenafil 20 mg 8 h prior to NTG resulted in a significant increase on HR and a small decrease in blood pressure.
(4) The effect of vardenafil 20 mg, 4 or 1 h prior to NTG produced a mean additional reduction of about 9 mmHg on systolic BP, about 6 mmHg on diastolic BP and 5 to 9 bpm increase in HR.
(5) These conclusions regarding the interaction of NTG with vardenafil contrast with those previously proposed following study 100304.
(6) It is possible that the hemodynamic interaction of vardenafil and NTG is dose-dependent.
(7) Co-administration of sildenafil (Viagra) with nitrates is contraindicated.

B.13 Reviewer's assessment/comments

(1) The co-administration of vardenafil with nitrates should be contraindicated due to a significant drop in blood pressure with concomitant use.

(2) The inclusion criteria for trial 10720 are acceptable. However, the number of men (healthy vs erectile dysfunction) is not included in the report. Theoretically, those with erectile dysfunction also have systemic vascular disease and may have a more profound hemodynamic response to study drug and NTG.

(3) The exclusion criteria for trial 10720 are acceptable. It is noted that patients with postural hypotension or low blood pressure have been excluded.

APPEARS THIS WAY
ON ORIGINAL

Appendix C: "A randomized, double-blind, placebo-controlled, period-balanced, two-part, three period crossover drug interaction study of vardenafil (10 mg and 20 mg) and terazosin (10 mg) in healthy males aged 45 to 75 to evaluate changes in blood pressure" (Trial 100480). Trial start date: October 1, 2002. Trial end date: October 29, 2002. Principal investigator: Maria Gutierrez, M.D. Study center: Comprehensive Neuroscience Inc., Fort Lauderdale, Florida.

Rationale for study: It is expected that many men who seek treatment for erectile dysfunction will require concomitant treatment for BPH. There is a potential for a drug-drug interaction between alpha antagonists and vardenafil both of which may cause hypotension.

C.1 Objectives: The primary objective was to compare changes in blood pressure, induced by vardenafil (10 mg and 20 mg) and placebo, in healthy male subjects when administered to subjects receiving the alpha-blocker terazosin (10 mg) at steady state. The secondary objectives were 1) to measure changes in heart rate until 6 hours after adminstration of study medication concomitant to steady state levels of terazosin; 2) to evaluate safety and tolerability; and 3) to evaluate the pharmacokinetics of terazosin and vardenafil.

C.2 Design and conduct summary: This was a Phase I, single-center, two part, randomized, period balanced, placebo-controlled, double-dummy, three-way crossover study. Parts I and II of the study were double-blind with respect to placebo, 10 mg vardenafil and 20 mg vardenafil. Terazosin was given in open-label fashion.

Subjects were uptitrated to a final dose of terazosin 10 mg during days 1 through 14 and continued to received 10 mg terazosin at 7 a.m. throughout Parts I and II of the study. On day 15, subjects began Part I, in which they were randomized to receive one of the following regimens over three sessions: (A) a single oral dose of 10 mg vardenafil; (B) a single oral dose of 20 mg vardenafil, (C) a single dose of vardenafil-matched placebo. At each session, vardenafil or placebo was dosed 6 hours after terazosin dosing (at approximately 1 p.m.) to achieve Cmax separation of six hours. There was a 48-hour washout period between study regimens.

All subjects were to participate in Part II beginning approximately 60 hours after the final dose of study medication in Part I. On day 22, subjects began Part II (7 a.m. vardenafil/placebo dosing *simultaneously* with terazosin to achieve simultaneous Cmax), in which they were randomized to receive one of the following regimens over three sessions (in addition to terazosin 10 mg): (D) a single oral dose of a vardenafil-matched placebo; (E) a single oral dose of 10 mg vardenafil; (F) a single oral dose of 20 mg vardenafil. Terazosin dosing and vardenafil or placebo dosing occurred at the same time (approximately 07:00). There was a 48-hour washout period between study regimens.

Reviewer's comment: The regimen key presented by the sponsor in the text above is inconsistent with the data result tables. For this review, the regimen key used will taken from the data result tables beginning on page 59 of the study report. The key is below.

Table C.1 Dosing regimens (Source- study report text, page 59)

Regimen	Study Drug-single dose	Timing
A	Placebo	6 hours after terazosin
B	Vardenafil 10 mg	6 hours after terazosin
C	Vardenafil 20 mg	6 hours after terazosin
D	Placebo	simultaneous with terazosin
E	Vardenafil 10 mg	simultaneous with terazosin
F	Vardenafil 20 mg	simultaneous with terazosin

The terazosin titration consisted of one mg on days 1-3, two mg on days 4-6, five mg on days 7-10 and ten mg on days 11-14. The first dose was given at bedtime (during an overnight stay in the clinic) to evaluate the possibility of a "first dose" effect. All subsequent dosing occurred at 7:00 a.m. as outpatients (except on day 2 when the patient was dosed before being discharged from the clinic). Patients reported to the clinic daily for orthostatic blood pressure and heart rate assessments pre- and 2-hour post-terazosin dosing. (Blood pressures and pulse rates were measured while subjects had been in a supine position for at least 3 minutes followed by repeat measurements after 3 minutes of standing). Fifteen minutes prior to study drug/placebo dosing, three baseline vital sign measurements were made. Following blood pressure measurements, a blood sample was drawn for pharmacokinetic analysis. Subjects were not to eat for 1 h before dosing to minimize any food effect. Additional blood samples (3 mL each) were collected for the determination of plasma terazosin and plasma vardenafil concentrations pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 h after terazosin and vardenafil dosing.

For Part II, after dosing, additional orthostatic blood pressure (supine and standing) measurements were taken once at each of the following times: 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 15, and 24 hours. Orthostatic blood pressures were always measured before blood sample collection.

Dietary restrictions: During each dosing session, subjects abstained from ingesting caffeine- or xanthine-containing products for 24 hours prior to the start of dosing until collection of the final blood pressure in Part II. During each dosing session, subjects abstained from alcohol for 24 hours prior to the start of dosing. Subjects were not allowed to drink grapefruit juice or eat grapefruit within 7 days prior to the first dose of study medication until the end of Part II. They also abstained from strenuous exercise for 48 hours prior to each study session until the completion of the session. During each dosing session, subjects ate all meals within 30 minutes. Subjects could drink water and other permitted beverages ad libitum throughout the study. Vardenafil/placebo and terazosin were given with 240 mL of water. Breakfast was served approximately 2 hours after terazosin dosing at 9:00 a.m. and lunch at 11:30 a.m.

Screening: Screening occurred within 30 days prior to administration of study medication. Screening included:

- Medical history.
- Complete medication history of all drugs taken (including the use of vitamins and herbal supplements; including St. John's Wort) at least 30 days prior to screening procedures.

• A history of alcohol use.
• Complete tobacco history including the type (e.g., pipe, cigar, chewing tobacco, or cigarette), quantity, and duration of use.
• Physical examination including height and weight, sitting vital signs (blood pressure, and heart rate).
• Standard 12-lead electrocardiogram (ECG).
• Following at least a 4-hour fast, blood and urine specimens for clinical laboratory safety tests were collected and a urine drug screen was performed.

Safety assessment: Orthostatic hypotension was defined as a reduction of systolic blood pressure of at least 20 mm Hg or diastolic blood pressure of at least 10 mm Hg within 3 minutes of standing. If orthostatic hypotension occurred prior to any dosing the subject was not to have been dosed. If orthostatic hypotension occurred following any dosing, the subject was observed carefully and/or discharged at the discretion of the Investigator. If at any time during the study, a subject's blood pressure was less than 100 mm Hg systolic and less than 60 mm Hg diastolic or the subject was symptomatic for hypotension, the subject was to have been withdrawn from the study. If at anytime during the study a subject had a systolic pressure less than 100 mm Hg and was symptomatic, the subject was to be treated with 500 mL-1,000 mL of intravenous normal saline at the discretion of the Investigator.

All adverse and serious adverse events were collected from the time the subjects signed the informed consent through the final study visit (follow-up visit).

Clinical laboratory safety tests and twelve-lead ECGs were performed at screening and at study follow-up.

Follow-up: All subjects returned for a follow-up visit 7 days after the final dose of study medication in Part II. At this visit subjects received a brief physical examination. Safety blood and urine tests and a 12-lead electrocardiogram (ECG) were also performed. AEs and partner pregnancy were also assessed at this time.

C.3 Study population:
Healthy male subjects between 45 and 75 years of age, and a body mass index between 19-34 kg/m^2 were eligible for the study. A total of 49 subjects were screened. Thirty subjects were enrolled (mean age=58).

Table C.2 Demographic Data

Parameter	Age (years)	Height (m)	Weight (kg)
n	30	30	30
Mean	58	1.7	76.5
SD	9.1	0.08	12.1
Range	45 - 74	1.58 - 1.88	51.4 - 99.5

100% male, 80% Hispanic, 17% White, 3% Black
Source: Study report, page 14

C.4 Inclusion and exclusion criteria

C.4.1 Inclusion criteria

1. Healthy male subjects between the ages of 45 and 75 years, inclusive.
2. Body mass index (BMI) between 19 and 34 kg/m^2, inclusive where:
BMI = (weight in kg)/ (height in meters)^2
3. The subject provides written informed consent.

C.4.2 Exclusion criteria

1. Treatment with any prescription or non-prescription drugs (including St John's Wort, vitamins, herbal and dietary supplements, as well as products containing grapefruit) within 7 days of the first dose of study medication and until the last study visit. Acetaminophen was permitted at doses of ≤2 g/day.
2. History of alcohol abuse/dependence within 6 months of the administration of the first dose of study medication. Alcohol abuse was defined as consumption exceeding, on average, 14 drinks/week for men (1 drink = 5 ounces of wine or 12 ounces of beer or 1.5 ounces of hard liquor).
3. History of illicit drug use as defined by a positive urine drug test at screening.
4. Treatment with an investigational drug within 30 days or five half-lives, whichever was longer, prior to the first dose of study medication (this included investigational formulations of marketed products).
5. Any clinically relevant abnormality identified on the screening history, physical or laboratory examination.
6. History of lightheadedness or syncope upon standing.
7. History of hypotension.
8. Systolic blood pressure greater than 160 mm Hg or diastolic blood pressure greater than 100 mm Hg.
9. Systolic blood pressure less than 100 mm Hg or diastolic blood pressure less than 60 mm Hg.
10. History of sickle cell anemia or disease.
11. History of retinitis pigmentosa.
12. Known history of allergy to PDE-5 inhibitors or terazosin.
13. Subjects not willing and able to follow the procedures outlined in the protocol or who are unable to provide written informed consent.
14. Blood collection of greater than 500 mL within 56 days prior to the start of the study.

Reviewer's comments: (1) The inclusion and exclusion criteria were acceptable. (2) It is noted that subjects with hypotension (defined as SBP <100 or DBP <60), hypertension (defined as SBP > 160 or DBP > 100), lightheadedness or syncope were excluded.

C.5 Primary and secondary endpoints

Pharmacodynamic:

Pharmacodynamic parameters comprised standing and supine systolic blood pressures, diastolic blood pressures and heart rate. Additionally, orthostatic systolic and diastolic blood pressures were calculated as standing minus supine values.

The *primary pharmacodynamic endpoint* was:

- Maximal change in standing systolic blood pressure from baseline within 6 hours of dosing with vardenafil 10 or 20 mg or placebo for p.m. dosing (Part I). The primary comparison of interest was between vardenafil 20 mg and placebo

following p.m. dosing (e.g., C - A) for the primary endpoint, maximal change in standing systolic blood pressure from baseline for p.m. dosing.

The *secondary pharmacodynamic endpoints* were:

- Maximal change in standing systolic blood pressure from baseline within 6 hours of dosing with vardenafil 10 mg or 20 mg or placebo for a.m. dosing (Part II).
- Maximal change in standing diastolic blood pressure from baseline within 6 hours of dosing with vardenafil 10 mg or 20 mg or placebo (a.m. and p.m. dosing).
- Maximal change in supine systolic and diastolic blood pressure from baseline within 6 hours of dosing with vardenafil 10 mg or 20 mg or placebo (a.m. and p.m. dosing).
- Maximal change in orthostatic (e.g., standing minus supine) systolic and diastolic blood pressure from baseline within 6 hours of dosing with vardenafil 10 mg or 20 mg or placebo (a.m. and p.m. dosing).
- Maximal change in standing and supine heart rate from baseline within 6 hours of dosing with vardenafil 10 mg or 20 mg or placebo (a.m. and p.m. dosing).

For blood pressure parameters, the maximal change was defined as the difference between the minimum blood pressure and the baseline blood pressure, and for heart rate parameters, as the difference between the maximum heart rate and the baseline heart rate. For all parameters, baseline was taken as the average of the three pre-dose (vardenafil/placebo) values for each regimen.

Pharmacokinetic: On day 1 of each session, blood samples for pharmacokinetic analysis of terazosin and vardenafil were collected from each subject up to 24-hours post-dose (predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24 hours) following drug administration in Parts I and II of the study.

Safety: Safety was assessed by blood pressure and heart rate measurements, adverse events, standard clinical laboratory safety tests and twelve-lead electrocardiograph (ECG). Clinical laboratory safety tests (CBC, liver panel, chemistry panel, UA) and twelve-lead ECGs were performed at screening and follow up only.

C.6 Withdrawals, Compliance and Protocol violations

C.6.1 Withdrawals

Two subjects (Subject 017 and Subject 028) withdrew during Part I of the study, leaving 28 subjects who completed all three sessions of Part I. Two subjects (Subject 011 and Subject 013) were withdrawn prior to the start of Part II of the study due to orthostatic hypotension BP 64/48 and esophageal ulcers/GERD, respectively, with a total of 26 subjects being dosed in the session 1 of Part II of the study. In total, twenty-eight subjects received Regimen A, 29 subjects received Regimen B, 28 subjects received Regimen C , 9 subjects received Regimen D, 8 subjects received Regimen E and 9 subjects received Regimen F. The study was terminated following the first session of Part II of the study due to the incidence of hypotension.

A total of 17 subjects withdrew from the study due to adverse events: one due to gastroesophageal reflux and esophageal ulceration, and 16 subjects due to episodes of hypotension or postural hypotension.

Reviewer's comment: There is a discrepancy between the above statement that can be found on page 14 of the study report and information on page 70 of the study report. Page 70 states that there were a total of 17 subjects withdrawn from the trial. Fourteen subjects had hypotensive events which were considered AEs. There were 3 additional subjects who had mild hypotension.

C.6.2 Compliance
Study medication was administered under the supervision of study personnel. The oral cavity of each subject was examined following dosing to assure that the study medication was taken. The amount taken by the subject, together with any related information (e.g., amount dispensed, returned) was recorded in the electronic CRF.

C.6.3 Protocol violations
The study was terminated following the first session of Part II of the study.

There were 194 protocol violations reported in 29 subjects during the course of the study. The majority of these events were episodes of low blood pressure, below the criteria outlined, for which the subject was not discontinued from the study. In addition to protocol violations associated with episodes of low blood pressure, there was one episode of a missed dose of vardenafil/placebo (subject 027) and one of double dosing with vardenafil/placebo (subject 010). Both subjects were given approval by the medical monitor to continue in the study; both subjects continued on their assigned randomization schedule. There were also several episodes of late dosing.

Sixteen subjects received medications or nutritional supplements during the study. The medications include mylanta, saline spray, iv normal saline, Prevacid, and Tylenol (which was permitted). The conditions treated were gastroesophageal reflux, heartburn, lower back pain and orthostatic hypotension.

These protocol violations were not considered sufficient by the sponsor to affect the conduct of the study nor did it represent a potential risk to the subjects during participation in the study or affect interpretation of the data. Excluding these subjects' data resulted in no change of inference (pharmacodynamic or pharmacokinetic) and as such, results are based on the full data set (e.g; an intent to treat analysis).

Reviewer's comment: The protocol violations regarding low blood pressure appear to be captured post hoc. This reviewer agrees with the rationale.

C.7 Pharmacodynamic analysis
Subjects 017 and 028 were not included in the statistical analysis due to insufficient data.

Run-in Phase (Days 1 to 14):
The following table (Table C.3) summarizes standing and supine mean (SE) blood pressure and heart rate prior to terazosin treatment and on Day 15 of terazosin treatment in the entire study population (n=30). There was a reduction in mean blood pressure values in subjects after terazosin alone.

Table C.3 Standing and supine mean (SE) blood pressure and heart rate prior to terazosin treatment and on Day 15 of terazosin treatment in the entire study population (n=30)

Parameter	Day 1	Day 15	
		Pre- terazosin a.m. dose	6 h post-terazosin a.m. dose
Standing Systolic BP (mm Hg)	138 (3.5)	120 (2.4)	113 (2.3)
Supine Systolic BP (mm Hg)	130 (3.1)	120 (2.2)	122 (2.3)
Standing Diastolic BP (mm Hg)	80 (1.9)	75 (1.4)	67 (1.5)
Supine Diastolic BP (mm Hg)	74 (1.5)	71 (1.3)	69 (1.4)
Standing HR (bpm)	71 (1.4)	75 (1.6)	75 (2.1)
Supine HR (bpm)	64 (1.3)	63 (1.4)	60 (1.6)

Source: Study report, page 19

Reviewer's comment: Following terazosin titration, SBP decreased by 18 mmHg, DBP decreased by 5 mmHg and HR increased by 4 bpm. Terazosin is known to have hypotensive effects and is indicated for the treatement of hypertension.

The subgroup of subjects who were reported with SAEs (n=17, subject 009 is included; subjects 017 and 028 are not included in the analysis due to insufficient data) appear to have had lower mean standing systolic blood pressure after 14 days of terazosin, compared to the study population as a whole and is illustrated in the following table (Table C.4).

Table C.4 Standing Mean (SE) BP and HR prior to terazosin treatment on day 1 and 15 of terazosin treatment in the subgroup of subjects reported with serious adverse events (n = 17*)

Parameter	Day 1	Day 15	
		Pre- terazosin a.m. dose	6 h post-terazosin a.m. dose
Standing Systolic BP (mm Hg)	136 (5.3)	116 (2.8)	109 (2.2)
Standing Diastolic BP (mm Hg)	81 (2.2)	73 (1.9)	65 (1.6)
Standing HR (bpm)	70 (1.7)	75 (2.1)	73 (1.9)

*Subject 009 included in the analysis; subjects 017 and 028 excluded from the analysis due to insufficient data

Reviewer's comment:. After terazosin titration in the subgroup experiencing SAEs compared to the entire population, the SBP does appear to be 4 mm Hg lower, the DBP appears to be 2 mmHg lower, but the heart rates are similar. However, the baseline values (prior to terazosin titration) for subjects who reported SAEs were similar to values for the entire study population. This fact leads to the conclusion that it is impossible to pre-determine which patients will have a hypotensive side effect based on baseline BP.

Part I (Vardenafil/placebo administered 6 hours after 10 mg of terazosin):
Following single doses of both 10 mg and 20 mg vardenafil, standing and supine, systolic and diastolic blood pressures were lower when compared to placebo.

Additionally, the magnitude of the effect for all parameters appeared to increase with increasing dose of vardenafil. A summary of the comparisons of interest for maximal change from baseline in standing blood pressure and heart rate are provided in the Table C.5 below:

Table C.5 Maximal change from baseline in standing blood pressure and heart rate- Part I

Parameter	Regimen	Means[1](SE)	Comparison	Point Estimate[2]	95% CI
Primary PD Parameter					
Standing Sys BP (mm Hg)[3]	A	-10(1.40)			
	B	-17(1.40)	B - A	-7	(-10,-3)
	C	-21(1.40)	C - A	-11	(-14,-7)
Secondary PD Parameter					
Standing Diastolic BP (mm Hg)[3]	A	-5(0.96)			
	B	-9(0.95)	B - A	-4	(-6, -1)
	C	-12(0.96)	C - A	-7	(-9, -4)
Standing HR (bpm)[4]	A	4(1.61)			
	B	11(1.60)	B - A	7	(3, 10)
	C	11(1.60)	C - A	7	(3, 10)

1 represents adjusted arithmetic mean from ANCOVA model
2 represents difference between adjusted arithmetic means
3 maximal change from baseline (minimum baseline)
4 maximal change from baseline (maximum baseline)
Note: above results are rounded to the nearest integer. (accounts for apparent discrepancies between means and point estimates and asymmetry of CI)
Regimen Key: A Placebo; B 10 mg Vardenafil; C 20 mg Vardenafil
Source: Study report, page 20

Reviewer's comments: An additional 7 mmHg (95% CI: -10, 3) and 11 mmHg (95% CI; -14, -7) decreases in standing SBP were seen for vardenafil 10 mg and vardenafil 20 mg, respectively, when given 6 hours after terazosin indicating a probable dose-response. Decreases were seen in DBP. Increases in HR of 7 bpm were also seen.

However, maximum changes in orthostatic systolic and diastolic blood pressure appeared to be similar to that of placebo. Following single doses of both 10 and 20 mg of vardenafil, standing and supine heart rates were higher as compared to placebo. The magnitude of the effects appeared to be similar for both 10 and 20 mg vardenafil. A summary of the comparisons of interest for maximal change from baseline for supine blood pressure and heart rate and orthostatic blood pressures are provided in the Table C.6 below:

Table C.6 Summary of the comparisons of interest for maximal change from baseline for supine blood pressure and heart rate and orthostatic blood pressures (secondary endpoints)

Parameter	Regimen	Means[1]	Comparison	Point Estimate[2]	95% CI
Secondary PD Parameter					
Supine Sys BP (mm Hg)[3]	A	-10(1.25)			
	B	-14(1.24)	B - A	-5	(-8, -2)
	C	-17(1.25)	C - A	-7	(-11, -4)
Supine Diastolic BP (mm Hg)[3]	A	-5(1.09)			
	B	-9(1.09)	B - A	-5	(-7, -2)
	C	-11(1.09)	C - A	-7	(-9, -4)
Supine HR (bpm)[4]	A	2(1.36)			
	B	7(1.36)	B - A	5	(1, 8)
	C	8(1.36)	C - A	6	(2, 10)
Orthostatic Sys BP (mm Hg)[3]	A	-13(1.50)			
	B	-14(1.50)	B - A	-1	(-5, 2)
	C	-14(1.50)	C - A	-1	(-5, 2)
Orthostatic Diastolic BP (mm Hg)[3]	A	-8(1.03)			
	B	-9(1.02)	B - A	0	(-3, 2)
	C	-10(1.03)	C - A	-2	(-4, 0)

1 represents adjusted arithmetic mean from ANCOVA model
2 represents difference between adjusted arithmetic means
3 maximal change from baseline (minimum minus baseline)
4 maximal change from baseline (maximum minus baseline)
Note: above results are rounded to the nearest integer. (accounts for apparent discrepancies between means and point estimates and asymmetry of CI)
Regimen Key: A Placebo; B 10 mg Vardenafil; C 20 mg Vardenafil Source: Study report, page 21.

Reviewer's comments: (1) This reviewer agrees that that based on data presented the orthostatic systolic and diastolic response of vardenafil 10 and 20 mg are similar to placebo. The explanation for this is unclear. During Part I of the study 8 subjects had a standing SBP < 85 mmHg and 27 subjects had a standing SBP < 100 mmHg (2) There is a heart rate response which does not appear to be dose-dependent.

Part II (Vardenafil/placebo administered concurrently with 10 mg of terazosin): The summary statistics for primary and secondary endpoints for Part II are provided below in Table C.7.

Table C.7 Summary statistics for primary and secondary endpoints are provided below

	Placebo n = 9	Vardenafil 10 mg n = 8	Vardenafil 20 mg n = 9
Standing SBP (mm Hg)			
Baseline	122 (13.7)	118 (13.9)	118(13.8)
Minimum			
Max Change from Baseline	-14 (13.1)	-37 (9.0)	-28 (14.5)
Mean Change from Baseline	4 (6.9)	-2 (8.0)	-4 (7.1)
Standing DBP (mm Hg)			
Baseline	77 (6.8)	71 (7.0)	75 (4.8)
Minimum			
Max Change from Baseline	-11(6.9)	-20 (5.8)	-20 (5.6)
Mean Change from Baseline	4 (6.4)	-0 (4.6)	-2 (5.6)
Standing Heart Rate (bpm)			
Baseline	75 (6.5)	76 (12.1)	72 (11.5)
Maximum			
Max Change from Baseline	19 (5.2)	24 (10.3)	28 (11.7)
Mean Change from Baseline	-6 (6.9)	-3 (8.1)	-3 (7.7)
Supine SBP (mm Hg)			
Baseline	132 (13.9)	118 (13.0)	120 (8.1)
Minimum			
Max Change from Baseline	-15 (10.1)	-22 (5.6)	-22(10.2)
Mean Change from Baseline	2 (8.1)	-2 (6.7)	-4 (7.7)
Supine DBP (mm Hg)			
Baseline	76 (5.5)	68 (8.3)	71 (4.8)
Minimum			
Max Change from Baseline	-11 (4.4)	-14 (5.2)	-16 (6.6)
Mean Change from Baseline	4 (5.6)	0 (5.1)	-3 (4.3)
Supine Heart Rate (bpm)			
Baseline	70 (7.4)	65 (7.8)	64 (8.7)
Minimum			
Max Change from Baseline	7 (7.4)	16 (9.5)	17 (6.4)
Mean Change from Baseline	-6 (5.5)	-4 (7.0)	-2 (4.9)
Orthostatic SBP (mm Hg)			
Baseline	-10 (13.1)	-0 (5.5)	-2 (7.5)
Minimum			
Max Change from Baseline	-8 (12.8)	-24 (10.2)	-22 (13.1)
Mean Change from Baseline	2 (8.4)	0 (8.8)	-0 (7.7)
Orthostatic DBP (mm Hg)			
Baseline	1 (5.8)	3 (2.1)	4 (4.4)
Minimum			
Max Change from Baseline	-6 (5.1)	-13 (8.0)	-12 (7.6)
Mean Change from Baseline	-0 (5.4)	-0 (5.1)	1 (4.6)

Source: Study report, page 22.

In Part II, similar trends as for Part I were observed for standing and sitting blood pressures and heart rates, with the magnitude of the effect appearing to be larger than that observed for Part I. However, unlike Part I of the study, maximal changes in orthostatic systolic blood pressure appeared to be larger following both doses of vardenafil than that of placebo.

Reviewer's comments: The trends in Part II are similar but the magnitude of affect is larger. Vardenafil 10 mg caused a 23 mmHg greater decrease compared to placebo in standing SBP in Part II compared to 7 mmHg in Part I. Vardenafil 20 mg caused a 14 mmHg greater decrease in standing SBP in Part II compared to 11 mmHg in Part I. DBP decreased 9 mmHg decrease with both vardenafil 10 and 20 mg relative to placebo in

Part II compared to 4 and 7 mmHg decrease in Part I. Heart rate increased by 5 and 9 bpm, with vardenafil 10 and 20 mg, respectively, in Part II, compared to 7 bpm with both 10 and 20 mg of vardenafil in Part I.

C.8 Pharmacokinetic analysis – See Clinical Pharmacology review

Part I: Based on the mean data, AUC and Cmax values for vardenafil increased approximately dose-proportionately (see Table C.8). The AUC and Cmax values observed following single oral 10 and 20 mg vardenafil administration were consistent with those observed previously in Phase I clinical trials.

Table C.8 Pharmacokinetics of vardenafil when dosed 6 hours after terazosin

PM Vardenafil Dosing (Part I)	N	AUC(0-t), ng.h/mL	Cmax, ng/mL	Tmax*, h
10 mg Vardenafil	28	34.6 (12.4)	7.42 (3.00)	2.00 (0.50-4.00)
20 mg Vardenafil	24**	73.6 (31.4)	15.4 (6.3)	2.00 (1.00-6.00)

* median (range)
** PK data for two subjects not available due to analytical difficulties; additionally one subject received two doses of 20 mg vardenafil and one subject had NQ values reported at all time points Refer to Section 4.7.
Source: Study report, page 17

Part II: Arithmetic mean (SD) vardenafil pharmacokinetic parameters following 10 and 20 mg vardenafil oral dosing simultaneously with 10 mg repeat oral terazosin administration to healthy male subjects are presented in the table below.

Table C.9 Pharmacokinetics of vardenafil when simultaneously with terazosin

a.m. Vardenafil Dosing (Part II)	n	AUC(0-t), ng.h/mL	Cmax, ng/mL	Tmax*, h
10 mg Vardenafil	8	29.5 (9.9)	9.31 (5.73)	1.00 (0.50-2.00)
20 mg Vardenafil	9	84.7 (38.7)	25.7 (10.2)	1.00 (0.50-1.50)

*median (range)
Source: Study report, page 18

Following steady-state oral administration of terazosin, maximum terazosin plasma concentrations generally occurred between approximately 0.5 and 1.0 hours post dose for each of the three regimens. Following single dose concurrent administration of 10 mg and 20 mg vardenafil with 10 mg repeat oral terazosin, maximum vardenafil plasma concentrations generally occurred between 0.5 to 1.5 hours post dose. Following Cmax, vardenafil plasma concentrations were generally quantifiable up to 16 hours postdose. Furthermore, vardenafil pharmacokinetic parameters for the two regimens were consistent with the results observed in Part I.

C.9 Safety analysis

C.9.1 Extent of exposure

Twenty-eight subjects completed all three sessions of Part I. Twenty-six subjects were dosed in session 1 of Part II of the study. The study was terminated following the first session of Part II of the study.

C.9.2 Deaths: There were no deaths during the study.

C.9.3 Adverse events

A total of 69 AEs were reported throughout the study (run-in period, Part I and Part II). The most common AE was hypotension, followed by headache, gastroesophageal reflux, somnolence and dyspepsia. Table C.10 gives an overview of AEs based on regimen.

Table C.10 Overview of Adverse events based on regimen

	Regimen						
	Run in	A	B	C	D	E	F
Total number of AEs	10	3	15	19	1	9	12
Most common AE: hypotension	0	0	0	0	1	6	6
Number of subjects with AEs	10	3	10	14	1	6	6
Number of subjects exposed	30	28	29	28	9	8	9

Source: study report page 14

Table C.11 gives a summary of all adverse events.

Table C.11 Summary of Adverse Events

Adverse Events (Preferred Term)*		Regimen					
	Uptitration	A	B	C	D	E	F
Hypotension					1	6	6
Headache	4		1	2			1
Gastroesophageal reflux			1	6			1
Dyspepsia				3		2	1
Somnolence	6						
Back pain		1	2	2			
Dizziness			4				1
Abdominal pain			1				
Creatinine phosphokinase increased				1			1
Diarrhea			1				
Dysphagia			1				
Esophageal ulceration			1				
Flatulence		1					
Hepatic function abnormal						1	
Hypotension postural		1	1	1			1
Pain				1			
Palpitation				1			
Rhinitis			1	1			
Vomiting			1	1			
Total Number of AE's	**10**	**3**	**15**	**19**	**1**	**9**	**12**
Total Number of Subjects Exposed	**30**	**28**	**29**	**29**	**9**	**8**	**9**
Number of Subjects with AE's	**10**	**3**	**10**	**14**	**1**	**6**	**6**

* Coded from verbatim term using Adverse Events Dictionary

A=Placebo; B=Vardenafil 10 mg; C=Vardenafil 20 mg; D=Placebo and Terazosin 10 mg;
E=Vardenafil 10 mg and Terazosin 10 mg; F=Vardenafil 20 mg and Terazosin 10 mg

Source: Study report, p. 64.

Reviewer's comment: There is a dose-related relationship to the number of adverse events.

A total of 17 subjects withdrew from the study due to adverse events: one due to gastroesophageal reflux and esophageal ulceration, and 16 subjects due to episodes of hypotension or postural hypotension.

Dizziness/Hypotension

AEs of dizziness were of interest in this study since these adverse events are often related to hypotension/postural hypotension. There were 6 AEs (4 in Part I and 2 in Part II)

related to dizziness; 5 were reported as dizziness and 1 was reported as postural hypotension.

Reviewer's comment: The cases were categorized based on the reported preferred term. Hypotension, dizziness and postural hypotension are reported separately.

Three subjects with dizziness-related adverse events in Part I experienced their adverse events after dosing with terazosin, but before dosing with vardenafil as follows:

> Subject 011 required Trendelenberg and intravenous normal saline treatment, 20 hours after placebo and 2 hours after terazosin on day 2 of session 3 in Part I. Blood loss from a disconnected intravenous catheter may have contributed to the event. The subject was discontinued from the study after this event (reported as symptomatic orthostatic hypotension).
>
> *Reviewer's comment: This 50 year-old male received vardenafil 20 mg (15 hours earlier) and terazosin (21 hours earlier) and had a standing BP 82/51. Two days later, after receiving placebo (20 hours earlier) and terazosin (2 hours earlier) had BP 64/48. His iv had come undone during sleep with an estimated blood loss of 100 cc. The above treatment was given at this point. The exacerbation of his blood pressure was most likely from the terazosin.*
>
> Subject 012 reported dizziness approximately 4 hours after a dose of terazosin, and prior to administration of 10 vardenafil, during Part I, session 3 of the study. At the time, the subject was not hypotensive. The subject continued in the study after this event.
>
> *Reviewer's comment: This 58 year-old male had a BP of 117/72 and a HR of 68 during the event. The dizziness resolved within 50 minutes. The cause of the dizziness is unclear based on the data available.*
>
> Subject 030 reported dizziness approximately 2 hours after terazosin in session 1 of Part I. At the time dizziness was reported, the subject was not hypotensive. The subject continued in the study after this event.
>
> *Reviewer's comment: This 74 year-old Hispanic male had dizziness approximately 3 hours after terazosin 10 mg with a standing BP of 114/74 and HR of 75. Symptoms resolved with oral fluids after approximately 4 hours. One week later, in part II, BP was 82/45, HR 73, forty-five minutes after simultaneous vardenafil 10 mg and terazosin 10 mg. The subject asymptomatic was discontinued from the study.*

Of the remaining three events of dizziness, one occurred in Part I of the study and two in Part II as follows:

> Subject 028 reported dizziness 30 minutes after vardenafil 10 mg, and six hours

after terazosin in Part I. The subject was discontinued from the study after this event did not receive any other study medication.

Reviewer's comment: This 64 year-old Hispanic male had a BP of 85/54 and a HR of 94 associated with dizziness. The dizziness resolved after approximately 4.5 hours. The subject had a previous episode of BP 90/56 and was asymptomatic. The subject was discontinued from the study.

Subject 006 had decreased standing blood pressure but was asymptomatic, one hour after vardenafil 20 mg co-administered with terazosin in Part II. Approximately 50 minutes later, the subject underwent phlebotomy, at which time he complained of dizziness.

Reviewer's comment: This 50 year-old Hispanic male had an asymptomatic supine BP of 99/62 and a standing BP of 84/67. Two days earlier his standing BP was noted to be 84/59 approximately 15 hours after vardenafil 10 mg and 21 hours after terazosin 10 mg. The subject was discontinued from the study.

Subject 027 reported dizziness 45 minutes after concurrent dosing with vardenafil 20 mg and terazosin 10 mg in Part II. The subject also complained of dizziness with reported orthostatic hypotension at the 1 hour post-dose blood pressure. The subject was treated with intravenous saline and placed in the Trendelenberg position.

Reviewer's comment: 62 year-old Hispanic male whose BP was 89/45, HR 83 during the event. He complained of dizziness and sweating. The event resolved after 15 minutes following 500 cc fluid bolus and Trendelenburg. The subject was discontinued from the study.

The majority of the above cases illustrate drug-related hypotension.

Gastroesophageal reflux
There were 8 episodes of gastroesophageal reflux (001, 007, 013, 020, 021, 024, 026, 030) during this study; all subjects except 021 and 030 were treated with an anti-acid and all episodes resolved.

Reviewer's comment: It is unclear why the incidence of gastroesphageal reflux was high in this trial. Review of the updated integrated safety summary does not show a similar finding in other trials.

Back pain
Five subjects experienced back pain during the study. Subject 024 experienced back pain after receiving placebo, subjects 002, 004 and 022 experienced back pain after receiving 10 mg vardenafil and subject 029 experienced back pain after receiving 20 mg vardenafil. All subjects were treated with Tylenol and all cases resolved prior to the end of

the study. All reported back pain AEs were mild in nature expect for Subject 022 who during session 1 of Part I, received 10 mg vardenafil (Regimen B) 6 hours post 10 mg terazosin. In session 2 of Part I, approximately 5 hours and 20 minutes after receiving terazosin (approximately 40 minutes prior to vardenafil 20 mg dosing), the subject complained of constant back pain. The back pain was severe in nature for approximately 1 to 2 hours and then lessened to mild. CPK and liver function tests were measured at the time of back pain and the results were all within the normal range (data on file-Comprehensive Neuroscience). The subject was treated with Tylenol. The back pain became mild and resolved after approximately 7 days. The subject was not withdrawn from the study due to this event and continued to received study medication. The subject received placebo in session 3 of Part I and 10 mg vardenafil with 10 mg terazosin simultaneously in session 1 of Part II. Additional doses of study medication did not worsen his existing back pain.

Reviewer's comment: The protocol synopsis (page 15 of the study report) states "creatinine phosphokinase levels measured post back pain were within the normal range." This discrepancy may be significant if the CK was collected "post back pain" which was "approximately 7 days" later. Consequently, a transient CK elevation could have been missed. The "data on file" referenced was not available for review. From a clinical perspective, the back pain could have been triggered from the vardenafil dosed in the prior period with all symptoms abating by the end of the study (possible de-challenge).

Laboratory abnormalities

Table C.12 gives a listing of all subjects with clinical laboratory values of potential clinical concern.

Table C.12 All subjects with clinical laboratory values of potential clinical concern.

Subject	Treatment	Parameter	Reference Range	BaselineValue	Time of Assessment	Value of Concern
003	Follow up	Glucose	65-109 mg/dl	113	Follow up	142
011	Screening	Hematocrit (PCV)	38.5 (50.0%)	NA	Screening	34.9
015	Follow up	Creatinine Kinase	0 - 200 IU/l	not done	Follow up	2213
017	Follow up	Creatinine Kinase	0 – 200 IU/l	not done	Follow up	792
018	Follow up	Hematocrit (PCV)	38.5 (50.0%)	39.1	Follow up	34.3
018	Follow up	Hematocrit (PCV)	38.5 (50.0%)	39.1	Follow up	35.4
018	Follow up	Hemoglobin	13.2 -17.1	13.2	Follow up	11.7
018	Follow up	Hemoglobin	13.2 -17.1	13.2	Follow up	11.9
026	Screening	platelets	140-400 K/UL	NA	Screening	536
026	Follow up	platelets	140-400 K/UL	536	Screening	518
029	Screening	Uric Acid	2.7 - 8.2 mg/Dl	NA	Screening	11.8
029	Follow up	Uric Acid	2.7 - 8.2 mg/Dl	11.8	Follow up	11.1

Source: Study report, page 72.

Three subjects (015, 017, 022) experienced laboratory abnormalities that were reported as adverse events. Two subjects had increased creatinine phosphokinase levels and 1 subject had increased alanine transaminase levels. The investigator considered none of these events related to study medication. None of these adverse events led to the stopping of study drug.

Reviewer's comments:
(1) Subject 015 had a CK of 2213 IU/l (baseline of 124 IU/l, 6 weeks prior). The AST was elevated at 58 IU/l (baseline 18 IU/l). The sponsor believes that the CK elevation was due to the subject's profession (construction worker). The degree of CK elevation for subject 015 suggests moderate muscle injury and should not result from day-to-day activities in light of a normal baseline value. This may represent a causal relationship to drug intake. No additional information has been submitted regarding this subject.
(2) Subject 017 had a CK of 792 IU/l with baseline of 128 IU/l, 5 weeks prior. Two weeks later the CK was down to 100 IU/l. The CK elevation of subject 017 does not cause clinical concern.
(3) Subject 022 had a ALT of 65 IU/l and 67 IU/l with a baseline of 8 IU/l, 5 weeks earlier. AST and total bilirubin were normal (32 IU/l and 0.4 mg/dl, respectively). The ALT elevation of subject 022 does not cause clinical concern. Subject 022 is not listed in the above table most likely due to the protocol defined value of potential clinical concern of >2 x the upper limit of reference range.
(4) Subject number 018 had a drop in Hb from 13.2 to 11.7. Subject 18 had one BP reading < 85 in Part I with vardenafil 20 mg. Systolic BP < 100 was noted in 4 out of the 6 sessions (Part I- A, B, C, Part II- E). No additional information was submitted.

Electrocardiogram data:
The sponsor believes there were no changes of clinical concern.

Reviewer's comment: ECG data were not presented in the study report or appendices.

C.9.4 Serious Adverse Events

SAEs were defined as any untoward medical occurrence that at any dose:
- Resulted in death.
- Was life-threatening.
- Required hospitalization or prolongation of existing hospitalization.
- Resulted in disability/incapacity.
- Was a congenital anomaly/birth defect.
- Medical or scientific judgement was exercised in deciding whether reporting was appropriate in other situations, such as important medical events that might not immediately have been life-threatening or resulted in death or hospitalization but could have jeopardized the subject or required medical or surgical intervention to prevent one of the other outcomes listed in the above definition.

Post hoc, the sponsor defined SAE as any episode of standing systolic blood pressure less than or equal to 85 mm Hg, symptomatic hypotension or hypotension requiring treatment.

There were no SAEs reported by the principal investigator during the study. Post hoc, the sponsor determined that any episode of standing systolic blood pressure less than or equal to 85 mm Hg, symptomatic hypotension and hypotension requiring treatment would be reported as a serious adverse event. As a result, a total of 19 SAEs were reported post hoc by the sponsor. A total of 18 subjects with SAEs defined as any episode of standing

systolic blood pressure less than or equal to 85 mm Hg and subjects with symptomatic hypotension or hypotension requiring treatment. A total of 14 subjects (003, 005, 006, 008, 011, 014, 015, 018, 022, 023, 024, 025, 027 and 030) experienced SAEs of standing systolic blood pressure less than 85 mm Hg. While subjects 009, 017 and 028 had standing systolic blood pressures equal to 85 mm Hg, these were also reported as SAEs by the sponsor. Additionally, the sponsor included subject 012 who experienced an episode of dizziness and the report of esophageal ulcers by subject 013 as SAEs.

Subject 009 (whose standing SBP was equal to 85 mmHg) was included in the group of subjects without SAEs because at the time of analysis, subject 009 was not considered to have experienced an SAE. In addition, subjects 017 and 028 were not included in the analysis due to insufficient data. The sponsor states that "there appeared to be no difference in the magnitude of maximal change of standing systolic blood pressure from baseline, following dosing with vardenafil/placebo, for Part I or Part II when comparing subjects with SAEs to those subjects who did not have SAEs." Subjects with SAEs tended to have lower baseline blood pressures prior to dosing with vardenafil/placebo than did those subjects who did not have SAEs.

The maximal change from baseline by regimen and occurrence of SAE for Part I is shown in Table C.13.

Table C.13 Maximal change from baseline by regimen and occurrence of SAE for Part I

Parameter	Regimen:	Subject w/o SAE (n = 12**) Baseline	Subject w/o SAE (n = 12**) Max. Change from Baseline	Subjects w/ SAE (n = 16*) Baseline	Subjects w/ SAE (n = 16*) Max. Change from Baseline
Standing Sys BP[1] (mm Hg)	A	118 (15.4)	-11 (8.4)	113 (9.3)	-11 (7.3)
	B	118 (7.9)	-17 (8.4)	111 (11.3)	-16 (10.4)
	C	122 (10.6)	-21 (7.8)	109 (11.9)	-21 (10.0)
Standing Dia BP[1] (mm Hg)	A	72 (7.6)	-8 (7.4)	65 (6.1)	-5 (4.5)
	B	69 (4.6)	-9 (4.5)	64 (6.8)	-8 (5.4)
	C	69 (7.8)	-12 (7.7)	63 (6.6)	-11 (5.3)
Standing HR[2] (bpm)	A	85 (10.2)	6 (6.0)	83 (11.5)	3 (8.3)
	B	90 (11.6)	10 (8.8)	84 (11.6)	11 (8.5)
	C	84 (9.8)	10 (5.9)	86 (10.4)	11 (12.1)
Supine Sys BP[1] (mm Hg)	A	122 (12.2)	-11 (9.6)	117 (13.3)	-10 (9.3)
	B	121 (10.8)	-16 (8.0)	114 (8.4)	-13 (8.2)
	C	118 (8.4)	-16 (9.0)	116 (10.2)	-17 (8.6)
Supine Dia BP[1] (mm Hg)	A	67 (7.8)	-7 (7.0)	62 (5.8)	-3 (6.2)
	B	66 (6.7)	-10 (4.4)	62 (5.3)	-8 (8.4)
	C	66 (8.0)	-10 (5.1)	64 (7.0)	-12 (7.7)
Supine HR[2] (bpm)	A	76 (7.2)	1 (5.8)	70 (6.7)	4 (8.8)
	B	78 (9.9)	7 (6.8)	73 (9.4)	6 (7.7)
	C	72 (9.2)	9 (6.9)	73 (8.3)	8 (7.5)

Note: Baseline is calculated using the average of 3 blood pressure measurements taken prior to dosing with vardenafil/placebo
* Subjects 017 and 028 are excluded from analysis due to insufficient data
**Subject 009 is included in subjects w/o SAEs since at the time he was not considered as having a SAE
1 maximal change from baseline (minimum minus baseline)
2 maximal change from baseline (maximum minus baseline)
Regimen Key: A Placebo, B 10 mg Vardenafil, C 20 mg Vardenafil
Source: Appendix J
Source: Study report, page 68.

Reviewer's comment: The magnitude of maximal change in standing SBP is similar for both groups (those with SAEs and those without). However, the absolute BP change is significant enough to cause clinical manifestations.

The maximal change from baseline by regimen and occurrence of SAE for Part II is shown in Table C.14.

Table C.14 Maximal change from baseline by regimen for Part II

Parameter	Regimen:	n	Baseline	Max. Change from Baseline
Standing Sys BP[1] (mm Hg)	D	9	122 (13.7)	-14 (13.1)
	E	8	118 (13.9)	-37 (9.0)
	F	9	118 (13.8)	-28 (14.5)
Standing Dia BP[1] (mm Hg)	D	9	77 (6.8)	-11 (6.9)
	E	8	71 (7.0)	-20 (5.8)
	F	9	75 (4.8)	-20 (5.6)
Standing HR[2] (bpm)	D	9	75 (6.5)	19 (5.2)
	E	8	76 (12.1)	24 (10.3)
	F	9	72 (11.5)	28 (11.7)
Supine Sys BP[1] (mm Hg)	D	9	132 (13.9)	-15 (10.1)
	E	8	118 (13.0)	-22 (5.6)
	F	9	120 (8.1)	-22 (10.2)
Supine Dia BP[1] (mm Hg)	D	9	76 (5.5)	-11 (4.4)
	E	8	68 (8.3)	-14 (5.2)
	F	9	71 (4.8)	-16 (6.6)
Supine HR[2] (bpm)	D	9	70 (7.4)	7 (7.4)
	E	8	65 (7.8)	16 (9.5)
	F	9	64 (8.7)	17 (6.4)

Source: Adapted from information in Table E9, page 768 of study report.

Reviewer's comment; The trends in Part II are similar to Part I but the magnitude of affect is much larger.

Outliers: For Part I, there were twelve subjects with a standing SBP < 85 mmHg- 1 with terazosin alone at steady state, 1 following terazosin + placebo, 3 following terazosin + vardenafil 10 mg, and 7 following terazosin + vardenafil 20 mg.
There were 77 subjects with a standing SBP < 100 mmHg- 6 in the terazosin run-in period, 3 prior to terazosin doing in part I, 21 prior to vardenafil/placebo treatment, 8 following terazosin + placebo, 20 following terazosin + vardenafil 10 mg, and 19 following terazosin + vardenafil 20 mg. For Part II, there were eight subjects with a standing SBP < 85 mmHg- 6 following terazosin + vardenafil 10 mg and 2 following terazosin + vardenafil 20 mg. There were 17 subjects with a standing SBP < 100 mmHg- 1 prior to vardenafil/placebo treatment, 1 following terazosin + placebo, 7 following terazosin + vardenafil 10 mg, and 8 following terazosin + vardenafil 20 mg.

C.10 Statistical analysis

Pharmacodynamic:
The primary and secondary endpoints were analyzed by analysis of variance (ANOVA) fitting terms for sequence, subject-within-sequence, period and regimen. Using the residual variance, point estimates and 95% confidence intervals for comparisons were obtained.

Target sample size: A sufficient number of subjects (30) were enrolled to ensure that 24 subjects completed the study. The sample size was based on feasibility. In a previous study, within-subject variability of maximal change from baseline in standing systolic blood pressure ranged from 11 mm Hg to 15 mm Hg. Based on these estimates and the

sample size of 24, the half width of 95% confidence interval for the difference between regimens would be 6.2 mm Hg and 8.8 mm Hg for the smaller and higher variabilities.

No formal statistical analysis of safety data was planned. Serious adverse events, defined as standing systolic blood pressure less than or equal to 85 mm Hg, symptomatic hypotension or hypotension requiring treatment were listed and summarized by time of occurrence (pre-dose terazosin, post-dose terazosin, pre-dose vardenafil 10 mg or 20 mg or placebo and post-dose vardenafil 10 mg or 20 mg or placebo). Occurrences of standing systolic blood pressure less than 100 mm Hg were summarized in a similar manner.

A post-hoc analysis was performed to better characterize the effects of vardenafil 10 mg and 20 mg administered 6 h after terazosin 10 mg compared with placebo. The average change from baseline of the 0-6 hour time course was calculated for standing and supine systolic and diastolic blood pressure, orthostatic systolic and diastolic blood pressure and standing and sitting heart rates.

Summary statistics (n, mean, standard deviation, minimum, median and maximum) were calculated by regimen for all primary and secondary endpoints from both Part I and II of the study.

Pharmacokinetic:
Subjects that completed the placebo session and at least one matching session within each part (a.m. or p.m. dosing) in which vardenafil was administered were included in the statistical analysis. Data from all subjects was listed.

The secondary endpoints (AUC and Cmax of terazosin) were analyzed by analysis of variance (ANOVA) fitting terms for sequence, period, subject (sequence) and regimen from Part I (p.m. dosing). Point estimates and corresponding 90% confidence intervals were constructed for the difference between regimens B/C and regimen A using residual variance. These were back-transformed to provide point estimates and corresponding 90% confidence intervals for the ratios.

C.11 Sponsor's conclusions
(1) Part I demonstrates an additional decrease in standing and supine systolic blood pressure, with small additional orthostatic changes in blood pressure, after vardenafil treatment on the background of terazosin. On average standing systolic blood pressure was 7 mm Hg and 11 mm Hg lower following a single dose of 10 mg and 20 mg vardenafil, respectively, relative to placebo. The magnitude of the effects of vardenafil on all blood pressure endpoints appeared to increase with increasing vardenafil dose. The sponsor states that the magnitude of the additional decrease in blood pressure with vardenafil in Part I is consistent with that observed in other studies of vardenafil alone.

Reviewer's comment: This reviewer has referenced two studies involving blood pressure measurements with vardenafil administration. Study 10348 (placebo controlled using vardenafil 20 mg and alcohol) showed a maximum change in systolic BP of 2.7 mmHg

(?supine). Study 100408 (placebo controlled study of cardiovascular response to exercise in patients with CAD using vardenafil 20 mg) showed a greater drop in systolic blood pressure in the post-exercise period after vardenafil treatment with mean changes form baseline at time points during exercise ranging from –1.4 to –6.7 mmHg for vardenafil compared with –0.9 to –2.3 for placebo. This reviewer was unable to confirm the sponsor's conclusion regarding consistency "with that observed in other studies of vardenafil alone".

(2) The trends observed for blood pressure changes in Part II (vardenafil/placebo administered concurrently with 10 mg of terazosin), were similar to that observed in Part I. However, orthostatic systolic and diastolic blood pressures appeared to be lower following vardenafil than that of placebo. Additionally, in general, the magnitude of the effects appeared to be larger than that observed in Part I. Standing and sitting heart rates for single doses of both 10 and 20 mg doses of vardenafil were higher as compared to placebo.
(3) Subjects with SAEs tended to have lower pre-dose blood pressure compared to those without SAEs.
(4) The findings of hypotension, with or without symptoms, during treatment at session 1 of Part II prompted discontinuation of the study.
(5) This study is likely to overestimate the risk of clinically significant hypotension following vardenafil administration to patients receiving chronic terazosin therapy. In medical practice, the titration pattern for terazosin dose that most patients will follow leads to a lower steady state dose.
(6) Separation of doses of terazosin and vardenafil 10 or 20 mg appears to reduce the pharmacological interaction described.

C.12 Reviewer's assessment/comments

(1) The combination of vardenafil 10 mg with terazosin 10 mg at steady state caused moderate hypotension (SBP < 85) in 3 out of 29 subjects (10%) with a 6-hour dose separation and 6 out of 8 (75%) subjects with simultaneous dosing. While the combination of vardenafil 20 mg with terazosin 10 mg at steady state caused moderate hypotension (SBP < 85) in 7 out of 28 subjects (25%) with 6-hour dose separation and 2 out of 9 (22%) subjects with simultaneous dosing.
(2) Six hour separation of doses did not negate the additive hemodynamic effects.
(3) The concomitant use of terazosin 10 mg and vardenafil 10 or 20 mg should be contraindicated.
4) The sponsor has proposed using vardenafil 5 mg in combination with alpha-blockers without dose/time time modification. No data was initially submitted to justify this combination. A 15-Day adverse event safety report dcoumenting dizziness and hypotension was submitted on April 28, 2003, on patient 100535-4012. This 62 year-old male in the vardenafil 5mg or placebo + terazosin trial experienced hypotension, dizziness and lightheadedness 1 hour following simultaneous administration of vardenafil 5 mg + terazosin 10 mg. His blood pressure was 80/60 and HR of 74, blood pressure prior to dosing was 126/79. He had a history of hyperlipidemia, HTN, BPH, and seasonal allergies. Concomitant medications were terazosin, calcium, proscar, ginko biloba. See

"Conclusion" section in Clinical Summary for a brief review of study 100535 which was submitted by the sponsor during labeling negotiations.

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