CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-400

Clinical Pharmacology and Biopharmaceutics Review

Clinical Pharmacology and Biopharmaceutics Review (Amendment)	
NDA:	21-400
Product Trade Name:	Levitra™
Active Ingredient:	Vardenafil hydrochloride (2.5, 5, 10 and 20 mg tablets)
Indication:	Male erectile dysfunction
Sponsor:	Bayer Corporation
Date of Submission:	February 19, 2003
Type of Submission:	Response to 'approvable' action
Reviewers:	Leslie Kenna, Ph.D., Sayed Al-Habet, Ph.D., and Dhruba J. Chatterjee, Ph.D.
Team Leader:	Ameeta Parekh, Ph.D.
Pharmacometrics:	He Sun, Ph.D.

I. Executive Summary

NDA 21-400 for vardenafil hydrochloride was issued an approvable letter on July 23, 2002. The approvable letter stated that it was necessary for the sponsor to rule out drug-related QT interval prolongation at therapeutic exposures and exposures resulting from known drug interactions that significantly increase systemic exposure to parent drug. The sponsor was requested to conduct clinical studies evaluating the degree of QT prolongation at plasma concentrations following the maximal potential interaction between vardenafil and CYP 3A4 inhibitors and to characterize the vardenafil plasma concentration-QT/QTc interval response relationship.

To address the issues leading to the "approvable action", among other studies, the sponsor provided Study 10929, "A Study to Evaluate the Effect of a Range of Single Oral Doses of Vardenafil and Sildenafil on Cardiac Conduction (QT/QTc prolongation)", in the current submission. Additionally, the sponsor submitted a report (Study 100512) to evaluate the pharmacokinetic interaction between ritonavir (a strong inhibitor of the liver CYP3A4 enzyme) and vardenafil. This amended OCPB review addresses findings primarily from these two studies and proposes final labeling OCPB recommendations reflecting the findings of this amendment along with the original OCPB review (finalized on 7/23/2002).

Study 10929 was a single dose, double blind, randomized, six-way crossover trial in 59 healthy males ranging from 45-60 years of age. Two doses of vardenafil were tested: 10 mg and 80 mg. The 10 mg strength represents the proposed recommended starting dose for vardenafil. The 80 mg strength was selected to cover the Cmax resulting from the drug-drug interaction between 5 mg vardenafil dosed with 600 mg BID ritonavir. Of the CYP 3A4 inhibitors tested, ritonavir had the most significant impact on vardenafil exposure.

Study 10929 revealed dose-related increases in QTc interval using all QT correction methods, however, the magnitude of that increase depended on the correction formula used. The scientific merit of the design and analyses of Study 10929 and the clinical significance of its results were discussed in a public meeting held by the Cardiorenal Drugs Advisory Committee on May 29, 2003. Specific questions posed to the committee included:

• Were the doses investigated adequate to evaluate the effect of vardenafil on cardiac repolarization?
• Was the duration of concentration and response sampling adequate to evaluate the effect of vardenafil on cardiac repolarization?
• Should the results with respect to one particular QT correction method be favored?
• Is it appropriate to set the 90% upper confidence limit for the mean change in QTc from baseline relative to placebo at 10 msec?

The above questions and other related issues are addressed in further detail in this review.

Members of the advisory committee expressed the following viewpoints:
• QT/QTc interval prolongation has limitations as a surrogate marker for Torsade de Pointes.
• It is currently unclear what level of QT/QTc increase is of clinical concern.
• Currently, no single method of QT correction can be considered most appropriate to evaluate the effect of drug on cardiac repolarization.
• Vardenafil causes QT interval prolongation, however, the magnitude of prolongation observed is not likely of clinical concern. Committee members stated that this opinion was influenced by both (1) postmarketing AERS and WHO database results for a drug in the same class and (2) the shallow dose-QT/QTc response relationship for vardenafil.
• It is useful to employ positive controls, such as moxifloxacin, in studies investigating QT prolongation. However, one must be mindful that the positive control serves as an indicator of assay sensitivity. The magnitude of the drug's effect on QT interval relative to moxifloxacin's effect on QT interval should *not* be used to justify any assumptions or predictions regarding the drug's safety.
• The effect of vardenafil on QT interval should be reported in its labeling.

The following results may be highlighted from the ritonavir PK drug interaction Study 100512:

- Based on geometric LS mean ratio, a 13- fold increase was observed in vardenafil C_{max} and 49 fold increase was observed in vardenafil AUC_{0-24} when 5-mg vardenafil was administered with ritonavir compared to vardenafil alone. The geometric LS mean ratio (vardenafil + ritonavir versus vardenafil alone) for $AUC_{0-\infty}$ was 108.3 (fold higher).
- Concomitant administration of vardenafil and ritonavir resulted in a significant increase in vardenafil half-life from 2.6 hours (given alone) and to 25.7 hours (administered with ritonavir). This was a 10-fold increase.
- Individual AUC_{0-inf} ratios were as high as >300 fold in the ritonavir + vardenafil arm as compared to vardenafil alone.
- With this resubmission, sponsor is additionally seeking approval of a 2.5 mg dose to aid in labeling restriction of vardenafil when combined with strong CYP3A4 inhibitors. Adequate labeling changes are being recommended (not to exceed a single 2.5 mg dose in a 72-hour period) to address this drug interaction issue. It is to be noted, however, that this 2.5 mg dose may provide the exposure (C_{max}) equivalent of about 30 mg dose when in combination with a potent CYP3A4 inhibitor such as ritonavir. Currently, 20 mg is the highest proposed dose.

Recommendation

The resubmission of NDA 21-400 for vardenafil hydrochloride is **acceptable** from the Clinical Pharmacology and Biopharmaceutics perspective, provided the labeling is changed as proposed.

II. Table of Contents

III. Summary of Clinical Pharmacology and Biopharmaceutics Findings:

IV. Question Based Review

What is the effect of vardenafil on cardiac repolarization at the recommended and supratherapeutic doses?
To address this issue, the sponsor provided Study 10929, "A Study to Evaluate the Effect of a Range of Single Oral Doses of Vardenafil and Sildenafil on Cardiac Conduction (QT/QTc prolongation)".

Study 10929

Design
Study 10929 is a single dose, double blind, randomized, six-way crossover trial in 59 healthy males ranging from 45-60 years of age. Study 10929 is placebo and active controlled. The active control is 400 mg moxifloxacin; a dose demonstrated to cause an increase in QT interval ranging from 7 to 12 msec. The sponsor also tested 2 doses of sildenafil, but the study was not powered for a formal statistical comparison between sildenafil and any other arm.

Table 1 shows the schedule for sample collection in each subject for each arm of Study 10929. The sponsor collected six replicate supine measures of QT interval and heart rate (HR) at thirty minutes, fifteen minutes, and immediately before dosing. The sponsor measured supine QT interval and heart rate, and drug concentration at each of five time points after treatment until 4 hours post-dose.

Time (hours)	QT, HR (# Measurements/Subject)	Treatment Concentration (# Measurements/Subject)
-.5	6	
-0.25	6	
0	6	
0.5	6	1
1.0	6	1
1.5	6	1
2.5	6	1
4.0	6	1

Table 1. Sample Collection Schedule in Each Subject for Each Arm of Study 10929.
Electrocardiogram data were collected in supine individuals and immediately before drawing the blood sample for concentration measurement, where applicable.

Rationale for dose selection
Two doses of vardenafil were tested in Study 10929: 10 mg and 80 mg. The 10 mg strength represents the proposed recommended starting dose for vardenafil. Selection of the 80 mg vardenafil dose was based on information regarding vardenafil's metabolism and drug-drug interaction potential. Vardenafil is metabolized by the cytochrome P-450 3A enzyme. Results of

studies investigating the effect of concomitant administration of vardenafil and various clinically relevant CYP3A inhibitors, specifically, (A) ritonavir, (B) erythromycin, (C) indinavir, and (D) ketoconazole, on vardenafil exposure are shown in Figure 1. Exposure is reported with respect to both Cmax and AUC. The orange (top) bar shows the ratio of the average maximum concentration of vardenafil when vardenafil is dosed with the interacting drug relative to when vardenafil is dosed alone. The blue (bottom) bar shows the ratio of the corresponding AUC values.

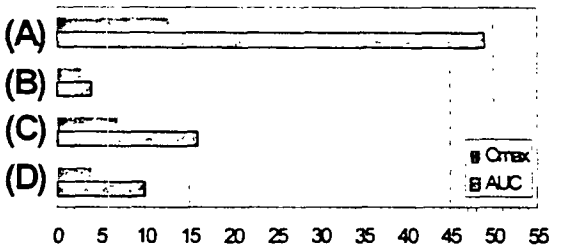


Figure 1. Vardenafil Drug-Drug Interaction Potential. Key to orange (top) and blue (bottom) bars: ratio of vardenafil Cmax and AUC, respectively, for vardenafil dosed concomitantly with a CYP 3A4 inhibitor versus vardenafil dosed alone. Regimens tested in interaction studies: (A) 5 mg Vardenafil + 600 mg BID Ritonavir, (B) 5 mg Vardenafil + 500 mg TID Erythromycin, (C) 10 mg Vardenafil + 800 mg TID Indinavir, and (D) 5 mg Vardenafil + 200 mg QD Ketoconazole. Note that 5 mg, 10 mg, and 20 mg are the sponsor's proposed single doses of vardenafil. Study 10929 investigated 10mg and 80 mg of vardenafil.

Figure 1 shows that a 5 mg dose of vardenafil coadministered with a 600 mg BID ritonavir regimen has the greatest impact on vardenafil concentration among the interactions with CYP 3A inhibitors investigated. Ritonavir causes a 12.7 fold increase in vardenafil's Cmax and a 49 fold increase in vardenafil's AUC.

Figure 2, a plot of vardenafil concentration as a function of time for the 10 and 80 mg doses and for the interaction study with ritonavir, shows how the 80 mg dose of vardenafil investigated in Study 10929 relates to the case of a drug-drug interaction with ritonavir. The green (diamond plotting symbol: ♦), blue (triangle plotting symbol: ▲), and red (filled circle plotting symbol: ●) lines show the **average** concentration of vardenafil after: a single 5 mg dose of vardenafil is administered alone, a single 5 mg dose of vardenafil coadministered with 600 mg BID ritonavir, and a single 80 mg dose of vardenafil is administered alone, respectively. For the 5 mg dose, vardenafil's **mean** Cmax is about 2 ng/mL, half life is about 3 hours, and AUC_{0-24} is about 7 ng*hr/mL. For the 5 mg vardenafil/600 mg ritonavir BID treatment, vardenafil's Cmax is about 30 ng/mL, half life is about 26 hours, and AUC_{0-24} is about 779 ng*hr/mL. For the 80 mg dose, vardenafil's Cmax is about 86 ng/mL, half life is 4 hours, and AUC_{0-24} is about 230 ng*hr/mL.

The 80 mg strength was selected to cover the Cmax resulting from the drug-drug interaction between 5 mg vardenafil dosed with 600 mg BID ritonavir. In agreement with **Figure 1**, Figure 2 shows that the **Cmax** reached when the 5 mg dose is taken with 600 mg ritonavir (30 ng/mL) is approximately 13 times higher than the maximum concentration measured when 5 mg of vardenafil is dosed alone (2 ng/mL). The **average** maximum concentration of vardenafil observed after an 80 mg dose (86 ng/mL) is administered is nearly 3 times greater than that observed when the 5 mg dose is coadministered with ritonavir. Thus, the choice of an 80 mg vardenafil dose

covers the Cmax expected when dosing 600 mg BID ritonavir with 5mg of vardenafil. Note however, that the concentration-time curve for 80 mg vardenafil dips below the curve for 5mg vardenafil + 600 mg BID ritonavir approximately 5 hours after dosing. The AUC of vardenafil when dosed with ritonavir (779 ng*hr/mL) is not covered by the AUC of the 80 mg vardenafil dose (230 ng*hr/mL). Vardenafil demonstrates saturable elimination for doses greater than 40 mg (a dose that is twice the highest proposed dose of vardenafil). This explains why the Cmax for the 80 mg dose (86 ng/mL) is disproportionately greater than the Cmax for the 5 mg dose (2 ng/mL). Based on linear kinetics, one would expect the Cmax for the 80 mg dose to be approximately 16 times (32 ng/mL) the Cmax for the 5 mg dose.

It is unknown whether Cmax or AUC is better correlated with QT response to vardenafil. Since the last sample in Study 10929 was collected at 4 hours post-dose, the design does not permit determination of the long-term effect of vardenafil on QT/QTc interval.

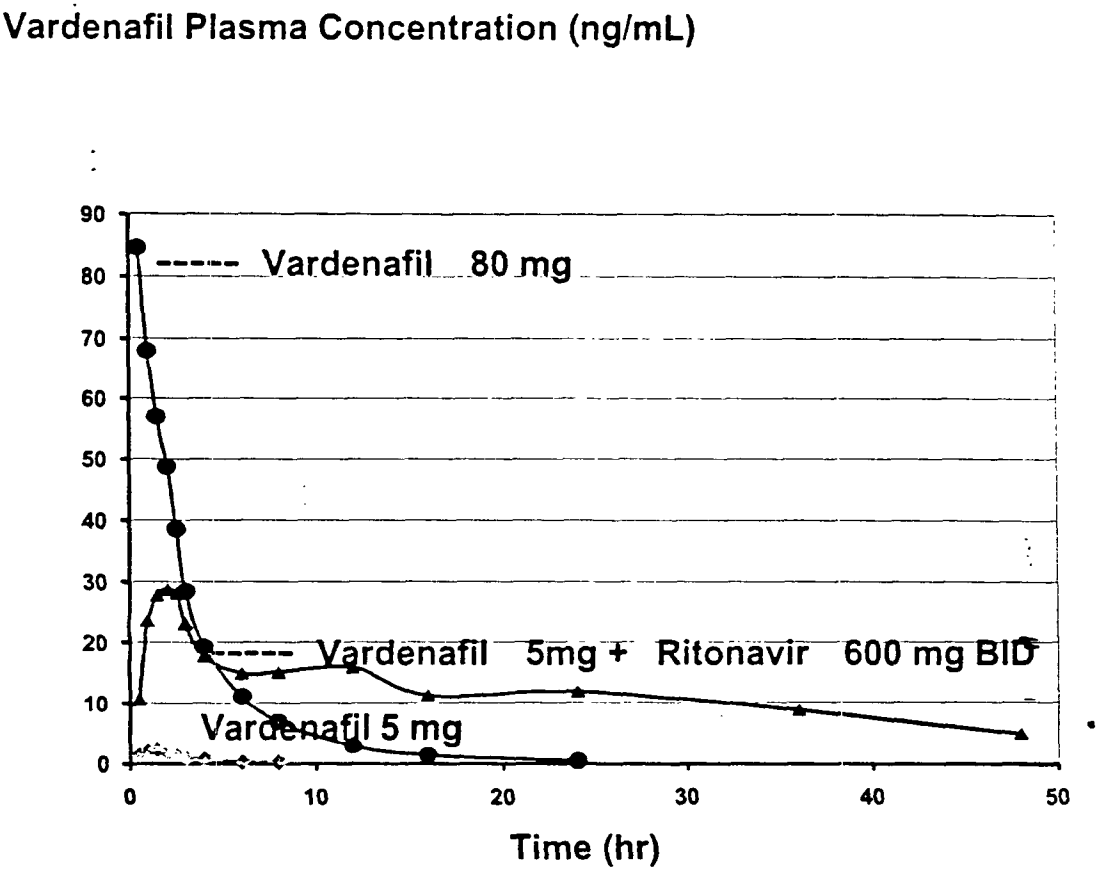


Figure 2. Concentration-Time Profile for Vardenafil 5 mg (diamond plotting symbol: ♦), Vardenafil 5 mg Coadministered with Ritonavir 600 mg BID (triangle plotting symbol: ▲), and Vardenafil 80 mg (filled circle plotting symbol: ●). The 80 mg dose of vardenafil in Study 10929 covers Cmax but not AUC for the interaction with ritonavir.

On average, the maximum concentration of vardenafil is reached 1 hour post-dose and Tmax ranges from 1 to 4 hours. Vardenafil's elimination half life ranges from 2 to 5 hours. Based on vardenafil's half life, a single dose given once daily should be nearly eliminated during the course of a day. This is confirmed by an accumulation ratio close to 1 for QD dosing. Given that vardenafil is taken on an as-needed basis, it is not likely to accumulate.

Pre-specified statistical goal.

The primary objective of Study 10929 was to exclude a greater than 10 msec effect of 80 mg vardenafil on QTc interval as compared to placebo. According to the QT/QTc concept paper[1] "drugs that prolong the QT/QTc interval by 5 to 10 msec under conditions of maximal effect have not been clearly associated with risk of arrhythmias. Drugs causing a mean 10-20 msec increase under conditions of maximal effect are of concern, but have been approved if they appear to have important therapeutic roles."

The primary endpoint for Study 10929 was defined as the change in Fridericia corrected QT interval (denoted QTcF) from baseline one hour post-dose. The one-hour time point was selected to reflect response at the average Tmax. The primary endpoint was considered met if the upper 90% confidence interval of baseline corrected QTcF for an 80 mg dose of vardenafil relative to placebo fell below 10 msec. That is, vardenafil was to be considered as not prolonging the QT interval if the upper 90% confidence interval for QTcF did not include 10.

Measured Heart Rate and QT interval

Table 2 shows the mean change in heart rate (HR: beats per minute) and QT interval (QT: milliseconds) from baseline 1 hour post-dose. It shows that vardenafil changes heart rate—there is a 2 beat per minute increase for the 10 mg dose and a 3 beat per minute increase for the 80 mg dose 1 hour after dosing. Note that placebo decreases heart rate relative to baseline by 3 beats per minute. Since vardenafil changes heart rate, it is necessary to correct measured QT interval for the confounding influence of a change in heart rate.

	Mean HR (bpm)	Mean QT (msec)
Vardenafil 10 mg	2 (1,3)	4 (2,5)
Vardenafil 80 mg	3 (2,4)	4 (2,6)
Moxifloxacin 400 mg	-1 (-2,0)	10 (8,11)
Placebo	-3 (-3,-2)	6 (5,7)
Sildenafil 50 mg	1 (0,2)	4 (2,6)
Sildenafil 400 mg	2 (1,3)	5 (4,7)

Table 2. Heart Rate and Uncorrected QT Interval for all Arms of Study 10929. Mean (90% CI) Change From Baseline 1 Hour Post-Dose.

[1]The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs; Preliminary Concept Paper. November 15, 2002.

Table 2 provides a snapshop of drug effect at the time point corresponding to the primary endpoint (1 hour post-dose). Plots of mean HR (Figure 3) and mean QT (Figure 4) as a function of time for vardenafil and control treatments reveal that neither mean heart rate nor mean QT interval peak at 1 hour for either of the vardenafil doses tested. Maximum mean HR for vardenafil is observed .5 hours post-dose. Maximum mean QT interval for vardenafil is observed 2.5 hours post-dose.

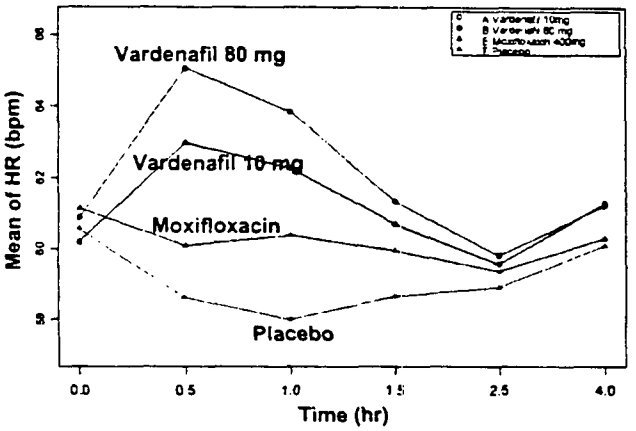


Figure 3. Mean Heart Rate as a Function of Time for Vardenafil and Control Arms. Maximum mean HR for vardenafil is observed .5 hours post-dose.

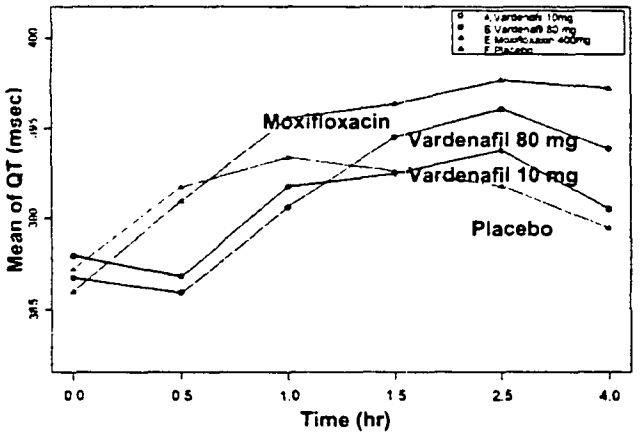


Figure 4. Mean QT Interval as a Function of Time for Vardenafil and Control Arms. Maximum mean QT interval for vardenafil is observed 2.5 hours post-dose.

QT correction formulas

The sponsor used 2 formulas to correct measured QT interval for changes in heart rate (HR): the **Fridericia Correction**

$$QTcF=QT/RR^{1/3} \quad (1)$$

and an **Individual Correction** using a linear model

$$QTcI = QT + b*(1-RR) \quad (2)$$

where RR is inversely related to HR and b is the slope of the regression line for each subject's "baseline" QT and RR data. The word baseline is in quotation marks to call attention to the sponsor's definition of baseline. The sponsor's definition of baseline consisted of measurements

taken before any treatment was given *and* measurements taken after dosing placebo. To be specific, the sponsor estimated each individual's slope "b" using the individual's 108 measurements of QT and RR taken before all treatments (6 replicates at 3 pre-dose time points for each of 6 arms) plus the 30 measurements (6 replicates at 5 post-dose time points) of QT and RR taken after placebo was dosed.

Since there is a difference in the effect of vardenafil versus placebo on heart rate (see Table 2 and Figure 3), an alternative linear individual correction method (**Individual Correction 2**; denoted **QTcI.2**) was explored during the process of reviewing this NDA. The QTcI.2 correction method uses the same formula (2) as the sponsor's Individual Correction method, however, each individual's slope "b" is estimated using only the measurements of QT and RR taken before any treatment was administered. That is, QTcI.2 involves estimating each individual's slope "b" using the 108 measurements of QT and RR taken before all treatments. Unlike QTcI, it does not include the 30 measurements of QT and RR taken after placebo is dosed.

Results will be presented in terms of three QT correction methods: the **Fridericia Correction (QTcF)**, the sponsor's **Individual Correction (QTcI)**, and the reviewer's **Individual Correction 2 (QTcI.2)**.

Results

Note that although the sildenafil results are presented, Study 10929 was not powered for a comparison between sildenafil and any other arm.

1. Mean Analysis

Table 3 shows the mean change in corrected QT interval (90 % and 95% confidence intervals) from baseline 1 hour post-dose *relative to placebo*. The placebo response subtracted out was 0.3 msec for QTcF, 2.0 msec for QTcI, and 2.1 msec for QTcI.2 values. Recall that moxifloxacin was included as an active control. The change in QTcF, QTcI, and QTcI.2 caused by moxifloxacin validates that the study was sensitive to detect changes in QTc of this magnitude (7 msec) or greater. Note that a dose-related increase in QTcF, QTcI, and QTcI.2 for vardenafil was observed. The magnitude of the response depends on the correction method used. There is a 7.7 msec increase in QTcF for the 10 mg dose and a 9.8 msec increase for the 80 mg dose. The individual corrections yielded smaller changes in QT prolongation—4.1 and 5.7 msec changes from baseline for the 10 and 80 mg doses, respectively.

The 90% confidence interval is reported in Table 3 because this confidence interval was specified as the primary endpoint. Table 3 also provides the results with respect to the 95% confidence interval. Note that the upper 90% confidence interval for the 80 mg vardenafil dose does not fall below the pre-specified criterion of 10 msec (QTcF upper 90% CI value: 11.14). That is, vardenafil did not achieve its primary endpoint.

	QTcF (Fridericia)	QTcI (Sponsor's Individual correction)	QTcI.2 (Reviewer's Individual Correction)
Vardenafil 10 mg	7.71 (90% CI: 6.30,9.14) (95% CI: 6.02,9.42)	4.13 (90% CI: 2.69,5.57) (95% CI: 2.41,5.86)	4.07 (90% CI: 2.51,5.64) (95% CI: 2.20, 5.95)

Vardenafil 80 mg	9.76 (90% CI: 8.37,11.14) (95% CI: 8.10,11.42)	5.79 (90% CI: 4.37,7.21) (95% CI: 4.09,7.49)	5.72 (90% CI: 4.13,7.31) (95% CI: 3.82,7.63)
Moxifloxacin 400 mg	7.65 (90% CI: 6.33,8.98) (95% CI: 6.07,9.24)	6.62 (90% CI: 5.30,7.93) (95% CI: 5.04,8.19)	6.71 (90% CI: 5.36,8.05) (95% CI: 5.09,8.32)
Sildenafil 50 mg	6.26 (90% CI: 4.82,7.70) (95% CI: 4.54,7.98)	3.84 (90% CI: 2.27,5.40) (95% CI: 1.96,5.72)	3.83 (90% CI: 2.22,5.44) (95% CI: 1.90,5.76)
Sildenafil 400 mg	9.03 (90% CI: 7.56,10.50) (95% CI: 7.27,10.79)	5.45 (90% CI: 4.31,6.60) (95% CI: 4.08,6.83)	5.50 (90% CI: 4.29,6.72) (95% CI: 4.05,6.96)

Table 3. Mean Placebo Corrected QTc Change (90% CI and 95% CI) from Baseline at 1 Hour Post-Dose. Mean placebo response was QTcF=0.3 msec, QTcI=2.0 msec, and QTcI.2=2.1 msec. Correction for placebo response involved subtracting 0.3 msec, 2.0 msec, and 2.1 msec from the mean QTcF, QTcI, and QTcI.2 response for each arm at 1 hour post dose, respectively. The 90% confidence interval is reported because this CI was defined as the primary endpoint. Note that the study is not powered for a comparison between sildenafil and any other arm.

Figure 5 and Figure 6 are the sponsor's plots of mean QTcF and mean QTcI as a function of time, respectively. Maximum mean QTcF occurs at 1 hour post-dose for both vardenafil strengths. Maximum mean QTcI occurs 1 hour post-dose for the 10 mg strength of vardenafil. Mean QTcI appears to plateau at 1 hour post-dose for the 80 mg strength of vardenafil.

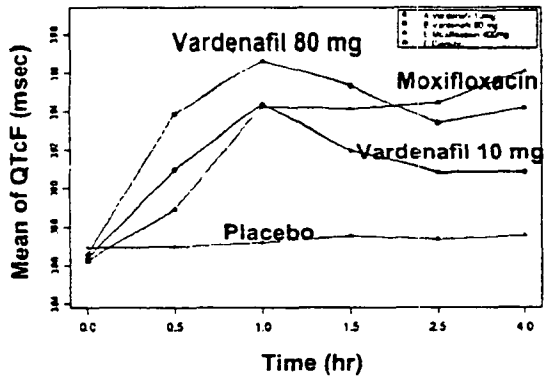


Figure 5. The Sponsor's Plot of Mean QTcF as a Function of Time for Vardenafil and Control Arms. Maximum mean QTcF occurs at 1 hour post-dose for both vardenafil strengths.

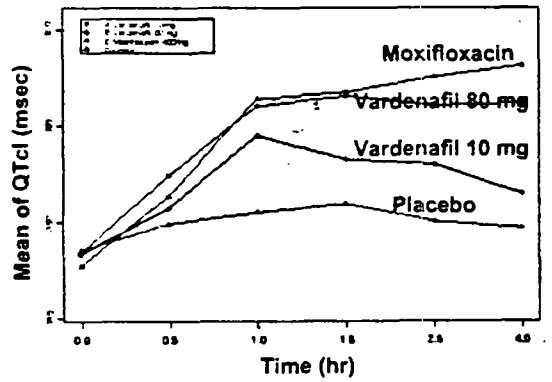


Figure 6. The Sponsor's Plot of Mean QTcI as a Function of Time for Vardenafil and Control Arms. Maximum mean QTcI occurs 1 hour post-dose for the 10 mg strength of vardenafil. Mean QTcI appears to plateau at 1 hour post-dose for the 80 mg strength of vardenafil.

2. Outlier Analysis

In addition to the primary analysis, an outlier analysis and an exploratory concentration-response analysis were submitted in support of the application. Key features of the outlier analysis are (1) the incidence of change in QTc from baseline greater than 30 msec and (2) QTc values greater than 450 msec. The concept paper[1] states that "drugs that prolong the mean QT/QTc interval by an amount greater than or equal to 20 msec have a substantially increased likelihood of being proarrhythmic." The concept paper considers a QT value greater than 450 msec in males to be "prolonged".

Table 4 shows the number (and percent) of subjects with one or more observation(s) of change in QTc from baseline greater than or equal to 30 msec after dosing. This table suggests that vardenafil causes a dose-related increase in QT prolongation. As with the mean analysis, the magnitude of vardenafil's impact on QT prolongation depends on whether the Fridericia or an Individual Correction method is used. According to the sponsor's analyses (QTcF and QTcI), for the 10 mg dose of vardenafil, there are either 7 or 2 subjects with an outlying value of QTc. For the 80 mg dose of vardenafil, there are either 9 or 4 subjects with an outlying value of corrected QT interval. The number of outliers after a 10 or 80 mg dose of vardenafil is greater than that for placebo. The sponsor noted that this chance in response is shallow given that there was, at most, a two-fold increase in QT interval (QTcI: 2 outliers versus 4 outliers) corresponding with an eight-fold increase in dose.

Note that no subject on any arm was observed to have a change in QTc from baseline ≥ 60 msec.

	QTcF	QTcI	QTcI.2
Vardenafil 10 mg	7 (12.1%)	2 (3.4%)	2 (3.4%)
Vardenafil 80 mg	9 (15.5%)	4 (6.9%)	8 (13.8%)
Moxifloxacin 400 mg	9 (15.5%)	10 (17.2%)	12 (20.7%)
Placebo	2 (3.4%)	1 (1.7%)	2 (3.4%)
Sildenafil 50 mg	5 (8.6%)	1 (1.7%)	2 (3.4%)
Sildenafil 400 mg	5 (8.6%)	2 (3.4%)	4 (6.9%)

Table 4. Number (Percent) of Subjects with at Least One Observed Change in QTc≥ 30 msec at .5, 1, 1.5, 2.5, or 4 hours post-dose. Note that each cell in the table reflects a total of 1740 data points collected in 58 subjects. No subject was observed to have a change from baseline of ≥ 60 msec.

The **Individual Correction 2** method yields results consistent with the results of the sponsor's individual correction for the 10mg dose of vardenafil (2 outliers), but consistent with the Fridericia correction for the 80mg dose of vardenafil (8 outliers). The **Individual Correction 2**

yields the same number of outliers for the 10 mg dose of vardenafil (2 outliers) as placebo (2 outliers).

The Fridericia correction method yielded an equivalent number of outliers for the 80 mg dose of vardenafil (9 outliers) and moxifloxacin (9 outliers). For both individual correction methods, there were fewer outliers for the 80mg dose of vardenafil (4 or 8 outliers) versus moxifloxacin (10 or 12 outliers). Note that there is a steeper dose-response relationship with QTcI.2 compared to QTcF and QTcI. For an eight-fold increase in dose, there is a four-fold (2 versus 8 outliers) increase in response.

Figure 7 presents the results of the mean and outlier analyses together. All subjects' baseline corrected QTcF values are plotted as a function of time. The orange (straight) line shows the cutoff for outlying measurements. Any points above this line are observations of baseline corrected QTcF greater than or equal to 30 msec. The average trend, or loess smooth, through the data is indicated by the blue line. This smooth is analogous to the mean response plotted in Figure 5, except that the response returns to baseline more gradually in Figure 7 than in Figure 5 as a result of the x-axis in Figure 5 not being spaced linearly with respect to the units of time.

It appears in Figure 7 that the maximum effect occurs on average 1 hour post-dose for both the 10 and 80 mg doses of vardenafil. For the 10 mg dose of vardenafil, the greatest number of outlying QTcF values are observed at 1 hour, thus correspond with mean Tmax. In contrast, it appears that the greatest number of outlying values occur at a time after mean Tmax for the 80 mg dose of vardenafil.

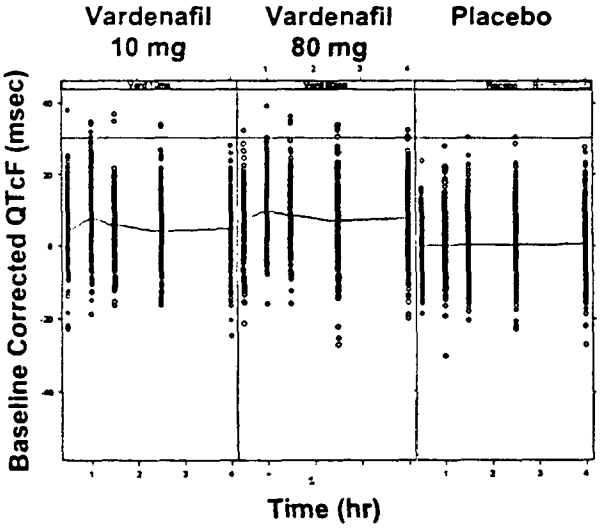


Figure 7. All Subjects' Baseline Corrected QTcF Values as a Function of Time. Key to plot: orange (straight) line drawn at 30 msec; blue line: loess smooth through all data.

Figure 8 is identical to Figure 7 except that it is a plot of all subjects' baseline corrected QTcI (not QTcF) values as a function of time. The figure shows a similar trend with respect to outliers as Figure 7—the majority of measurements of QTcI $\geq$ 30 msec corresponds with Tmax (1 hour) for the 10 mg vardenafil dose and the majority of outliers occurs after mean Tmax for the 80 mg

dose. However, Figure 7 and Figure 8 show some differences with respect to the mean response. According to QTcI, it is unclear whether the maximum response has been achieved by the end of the collection period for the 80 mg dose.

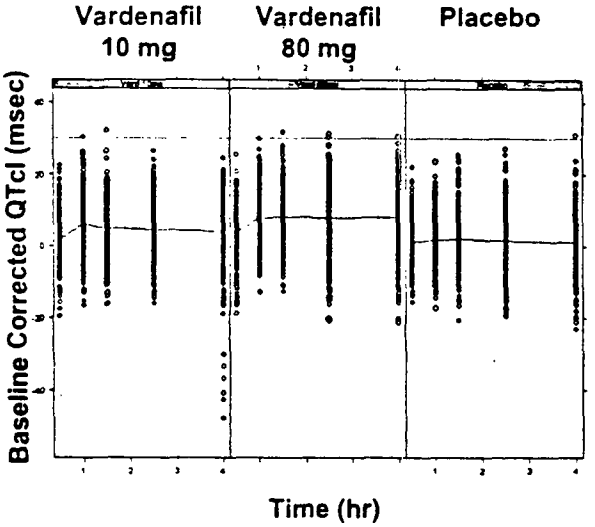


Figure 8. All Subjects' Baseline Corrected QTcI Values as a Function of Time. Key to plot: orange (straight) line drawn at 30 msec; blue line: loess smooth through all data.

Figure 9, a plot of QTcI.2 versus time, shows a similar average and outlier trend as Figure 8 (for QTcI). However, it shows that QTcI.2 yields more outlying values than QTCI.

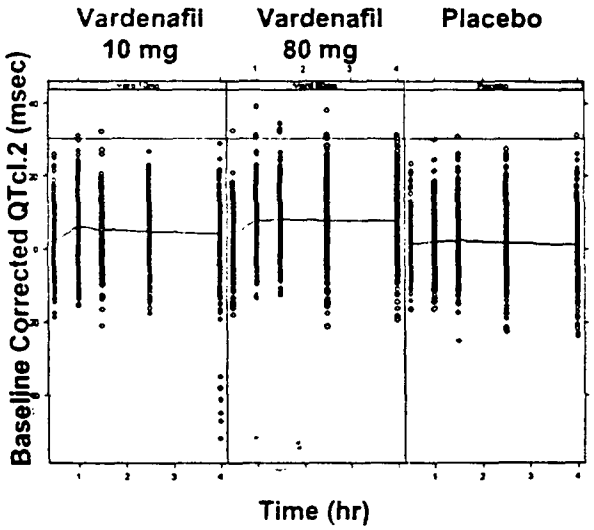


Figure 9. All Subjects' Baseline Corrected QTcI.2 Values as a Function of Time. Key to plot: orange (straight) line drawn at 30 msec; blue line: loess smooth through all data.

Table 5 shows the number of subjects with at least one measurement of QT/QTc interval greater than 450 msec post-dose. No subject receiving the 10 mg dose of vardenafil had a corrected QT value greater than 450 msec. This is equivalent to the response to placebo. The number of

outlying uncorrected QT values for the placebo arm (3 outliers) was greater than the number of outlying QT values for 10 mg vardenafil (2 outliers). The number of outlying QT values for the 80 mg dose (4 outliers) was similar to moxifloxacin (5 outliers). According to the individually corrected values, one subject receiving the 80 mg dose of vardenafil had an outlying value. This was greater than that observed for placebo (0 outliers) and less than that observed for moxifloxacin (2 outliers). Note that the one subject who had this QTcI and QTcI.2 value greater than 450 msec dropped out of the study after receiving only 80 mg vardenafil and 50 mg sildenafil. No subject on any treatment had QTcF greater than 450 msec.

	QT	QTcF	QTcI	QTcI.2
Vardenafil 10 mg	2	0	0	0
Vardenafil 80 mg	4	0	1*	1*
Moxifloxacin 400 mg	5	0	2	2
Placebo	3	0	0	0
Sildenafil 50 mg	2	0	1*	1*
Sildenafil 400 mg	2	0	0	0

Table 5. Number of Subjects With at Least One Observation of QT/QTc Interval Greater than 450 msec Post-Dose. The values superscripted with an asterisk (*) are observations from a single subject who withdrew from the study after receiving doses of 80 mg vardenafil and 50 mg sildenafil only.

Table 6 shows the results of this outlier analysis with respect to the number of observations of QT/QTc interval greater than 450 msec post-dose.

	QT	QTcF	QTcI	QTcI.2
Vardenafil 10 mg	2	0	0	0
Vardenafil 80 mg	43	0	2*	2*
Moxifloxacin 400 mg	51	0	2	3
Placebo	39	0	0	0
Sildenafil 50 mg	38	0	19*	19*
Sildenafil 400 mg	8	0	0	0

Table 6. Number of Observations of QT/QTc Interval Greater than 450 msec Post-Dose. The values superscripted with an asterisk (*) are observations from a single subject who withdrew from the study after receiving doses of 80 mg vardenafil and 50 mg sildenafil only.

Evaluation of QT Correction Methods

The results, thus far, show that the magnitude of the effect of vardenafil on QT interval with respect to both mean and outlier analyses depends on the correction formula used. That raises the

question *which result better reflects the influence of vardenafil on cardiac repolarization?* One tool for making that decision is to select the method yielding corrected QT values that are independent of heart rate or RR interval. This can be evaluated by determining which method yields QTc values for which the slope of the QTc versus RR relationship is closest to zero.

The sponsor submitted scatterplots of QTcF versus HR (Figure 10) and QTcI versus HR (Figure 11) for the 10 and 80 mg doses of vardenafil. There is less of a trend in Figure 10 than in Figure 11, suggesting that QTcF is the more successful correction method.

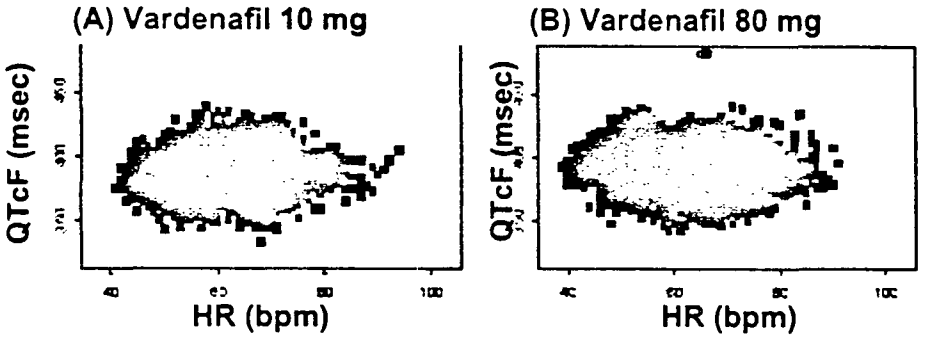


Figure 10. All values of QTcF Plotted as a Function of HR. The data suggest that there is no trend relating QTcF and HR.

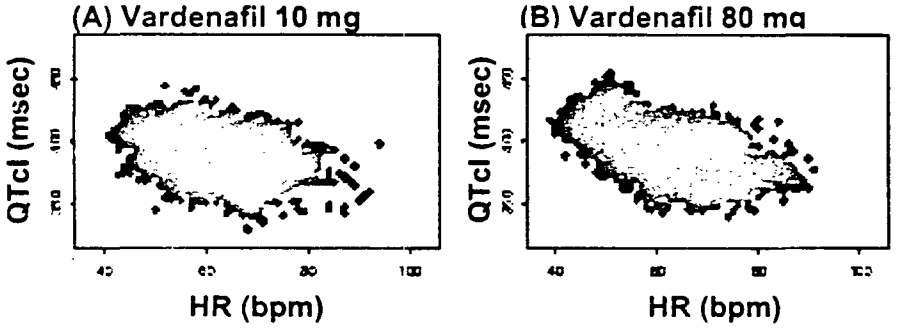


Figure 11. All values of QTcI Plotted as a Function of HR. The data suggest that there is a negatively sloping trend between QTcI and HR.

Another approach to determining if no relationship between corrected QT and RR intervals remains was explored during the review process. In addition to evaluating whether the corrected QTc values are independent of RR when the data from all subjects are pooled, one may estimate the slope of the QTc/RR relationship for each individual. That is, a separate slope can be computed using each subjects' QTc and RR data.

Figure 12 shows the regression line (linear correlation) fit to the pooled (A) QTcF, (B) QTcI, and (C) QTcI.2 versus RR data. Figure 13 shows a scatterplot of the individual slopes (1 for each of 59 subjects) for each subjects' (A) QTcF, (B) QTcI, and (C) QTcI.2 versus RR data.

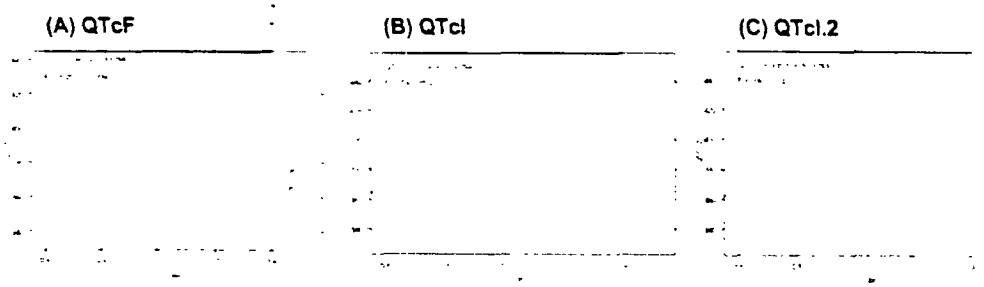


Figure 12. Regression Line Fit to All Subjects' (pooled) QTc and RR data. See Table 7 for the parameters of the fit.

Figure 13. A Scatterplot of Each Individual's QTc versus RR Regression Line Slope. Note the difference in scale on the y-axis for each correction method. See Table 7 for the parameters of the fit.

Table 7 summarizes the results of both methods of evaluation (pooled and individual QTc versus RR slope). The Fridericia correction yields a slope (3.8) closest to zero for the pooled QTc/RR data (QTcI: 52; QTcI.2: 58). The individual correction methods yield slopes closer to zero (mean QTcI slope: -1.9×10^{-11}; mean QTcI.2 slope: -1.4×10^{-14}) than the Fridericia method (mean QTcF slope: -49) when each subjects' QTc/RR data are regressed.

	QTcF	QTcI	QTcI.2
Fit pooled QTc/RR data	3.8	52	58
Fit individual QTc/RR data	Mean: -49 Range:	Mean: -1.9×10^{-11} Range:	Mean: -1.4×10^{-14} Range:

Table 7. Slope(s) of QTc versus RR for "Baseline" Data.

Note that the pooled method of validation assumes that all of the points in the plot are independent. This assumption may be incorrect if any individual has more than one data point. Here, subjects have over 100 data points.

3. Concentration-Response Analysis

The sponsor performed an exploratory analysis to investigate the concentration-response relationship between vardenafil and QTcF.

The sponsor plotted each subjects' mean QTcF values as a function of concentration then visually inspected the plots for indications of hysteresis. The sponsor noted hysteresis in some plots, but also observed that for a large number of subjects, maximum QTcF interval coincided with Cmax. Figure 14 gives examples of the types of plots supporting the sponsor's decision to use a direct effects PK/PD model.

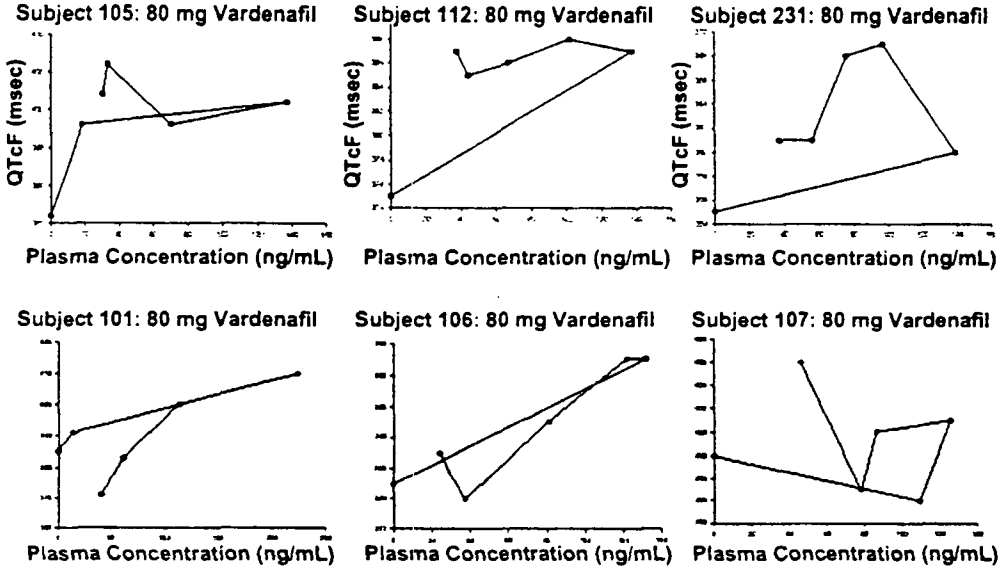


Figure 14. QTcF as a Function of Concentration for 6 Subjects. These are a sample of plots the sponsor used to evaluate whether a direct effects model was appropriate.

Given the wide variability in QTcF measurements and the relatively short duration of sampling beyond Tmax (Tmax range: 1-4 hours), these data are not well suited for fitting a dynamic model.

The sponsor performed a population PK/PD analysis of all of the QTcF data and reported that an Emax model fit the vardenafil and sildenafil data significantly better than a linear model, while a slope-intercept model fit the moxifloxacin data significantly better. The sponsor estimated only one Emax parameter for both vardenafil and sildenafil, assuming that Emax is the same for these two drugs. The sponsor's model also assumed that inter-individual variability (IIV) in EC50 for sildenafil and vardenafil are equivalent. Figure 15 shows the observed and predicted values of QTcF for the sponsor's Emax model as a function of vardenafil concentration for the 10 mg (inset plot) and 80 mg (main plot) doses. Table 8 reports the parameters corresponding specifically to the vardenafil (Emax, $EC50_V$), sildenafil (Emax, $EC50_S$) and moxifloxacin (S_M: slope) data as well as parameters applicable to the entire data set (E_0, IOV on E_0, Random Residual Variability).

According to the sponsor's model, QTcF increased with increases in plasma concentration for vardenafil with response plateauing at higher plasma concentrations. The population PD parameters for this model were such that the standard errors (% CV) were less than 35% for all of the parameters. The baseline QTcF response (E0) in absence of any drug administration was 387 msec. The inter-individual variability (IIV) in E0 was approximately 3.2% (equivalent to

12.4 msec) while the interoccasion variability in E0 across the six occasions was approximately 1.8%(7 msec). The estimated maximal increase in QTcF following administration of vardenafil and sildenafil was 8.29 msec with an IIV of approximately 25%. The concentrations of vardenafil and sildenafil resulting in half-maximal effect (EC50) on QTcF were approximately 2.44 and 59.2 ng/mL, respectively with an IIV (assumed to be the same for vardenafil and sildenafil) of approximately 120%.

Figure 15 shows that there was considerable scatter of the individual QTcF responses around the population predicted concentration-effect relationships. The sponsor attributes this to the large between-day variability in the baseline QTcF as well as large inter-subject variability in baseline and drug response. Note that according to the sponsor's chart of parameter values (Table 8), the "large" between drug variation in baseline QTcF (IOV on E0) and the "large" intersubject variability in baseline and drug response were 3.19% and 25.2%, respectively.

The results in Table 8 show that EC50 values were not well estimated. The sponsor attributes this to a lack of data at low concentrations. Alternatively, this may reflect model mispecification in assuming that vardenafil and sildenafil have the same interindividual variability in $EC50_V$ and $EC50_S$.

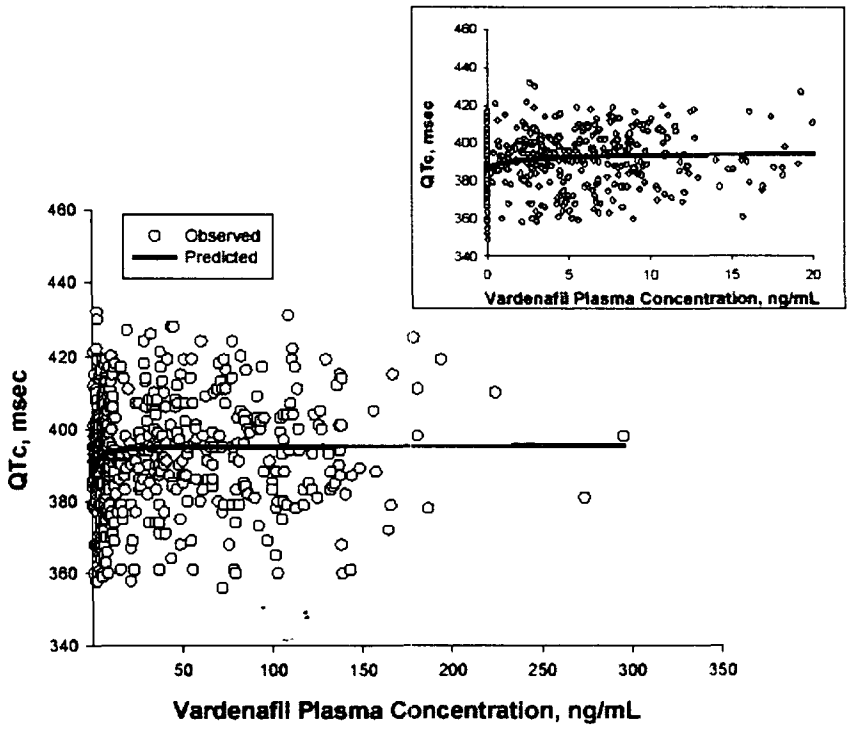


Figure 15. Sponsor's Plot of Observed and Predicted QTcF Values as a Function of Vardenafil Plasma Concentration. The large graph is a plot of data collected after dosing 80 mg vardenafil. The inset graph is a plot of data collected after dosing 10 mg vardenafil. Note: the sponsor fit the model to data from all study arms simultaneously.

Parameter	Population Mean (% CV[a])	% Inter-Individual Variability (% CV[a])
E_0 (msec)	387 (0.43)	3.19 (18.9)
Emax (msec)	8.29 (6.10)	25.2 (46.4)
$EC50_V$ (ng/mL)	2.44 (34.4)	120.4 (58.1)
$EC50_S$ (ng/mL)	59.2 (33.6)	120.4 (58.1)
S_M (msec*mL/ng)	0.00347 (7.81)	38.9 (41.1)
IOV on E_0*	1.80 (7.68)	
Random Residual Variability** (%CV)	4.00 (7.00)	

* IOV expressed as % coefficient of variation

** expressed as msec

[a] Precision expressed as % coefficient of variation

Table 8. The Table of Sponsor's Values of Vardenafil Model Parameters. Note: the sponsor fit the model to data from all study arms simultaneously.

The sponsor's goodness of fit assessment included plots of (1) observed QTcF versus the population predicted QTcF for all data, (2) weighted residuals versus the predicted QTcF values for all data, (3) weighted residuals with respect to subject ID for all data, and (4) individual predicted versus observed QTcF values for all data. To summarize the information presented in the plots: there was fairly uniform, but wide, variability around the line of identity in the plot of observed QTcF versus the population predicted QTcF. The plot of weighted residuals versus the predicted QTcF values appeared widely scattered, but, relatively uniformly distributed around zero. The plot of weighted residuals with respect to subject ID suggests that no single subject contributes substantially to the observed variability. The sponsor suggested that the scatter around the line of unity is due to the fact that the population PK/PD model does not take into account the variability terms. Figure 16 shows the sponsor's plot of individual predicted versus observed QTcF values.

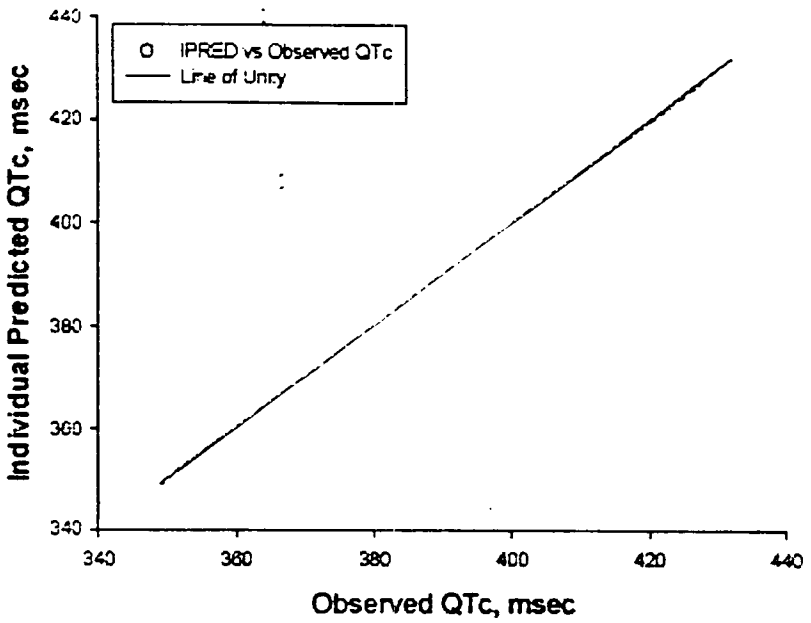


Figure 16. Individual Predicted QTcF Versus Observed QTcF for the Sponsor's Final Model. Note: the sponsor fit the model to data from all study arms simultaneously.

The sponsor performed a "Posterior Predictive Check" to validate the model. The sponsor performed 250 simulations to evaluate the probability that the observed QTcF values lay within the 2.5-97.5th percentile of simulated predicted QTcF values. The results of this analysis are reported in Table 9 and shows that 91.2-98.2 of the observed data fell within the 95% confidence interval. Note that the vardenafil data (REG A and REG B in Table 9) was the least compatible with the model, having means furthest from 95 (REG A at 2.5 hours: 91.2 and REG B at 2.5 hours: 91.4), while placebo was described best (REG F in Table 9), having an overall mean closest to 95 (94.7). Overall, the mean for all data was equivalent to 95.

timepoint	0 hr	0.5 hr	1 hr	1.5 hr	2.5 hr	4 hr	Mean by Regimen
REG A							93.9
REG B							93.4
REG C							95.7
REG D							97.1
REG E							93.9
REG F							94.7
			Overall Mean				94.8

Table 9. Sponsor's Model Validation Via Posterior Predictive Check: Percentage of the Observed Data Falling Within the 95% Confidence Interval Based on 250 Simulated Studies. Note that REG A = vardenafil 10 mg, REG B = vardenafil 80 mg, REG C = sildenafil 50 mg, REG D = sildenafil 400 mg, REG E = moxifloxacin 400 mg, REG F = placebo.

The sponsor modeled all data from all treatment arms simultaneously and constrained the Emax for vardenafil to be equivalent to the Emax for sildenafil. In the process of this review, an

exploratory concentration-response analysis of data from the vardenafil treatment arms only (10 mg and 80 mg) was performed. The fit of a linear and Emax model to the QTcF data was compared. The same models were fit to the QTcI data and compared. The mixed effects linear model reported here had $QTcF_{BASE}$ (and $QTcI_{BASE}$) and Slope as fixed effects and Slope as a random effect. The mixed effects Emax model reported here had $QTcF_{BASE}$ (and $QTcI_{BASE}$), $QTcF_{MAX}$ (and $QTcI_{MAX}$), and EC50 as fixed effects and $QTcF_{BASE}$ (and $QTcI_{BASE}$) as a random effect.

Model for QTcF Data

The log likelihood for the QTcF data with respect to the mixed effects linear model versus the mixed effects Emax model was -19919.9 versus -19993.2, respectively. The Emax model yielded a significantly better fit to the data than the linear model with $p<.05$. Figure 17 and Figure 18 show the individual and population fit to each subjects' vardenafil data. Although there is a statistically significant improvement in the Emax versus linear model, it is unclear from visual inspection whether the Emax model yields any benefit relative to the linear model. Figure 19, the plot of the residuals for the Emax model, shows an increasing trend in response (rather than the desired random scatter) with concentration for some subjects. This suggests that several subject's data are poorly described by an Emax model. Closer inspection reveals that these subjects did not reached Emax during the course of the study.

Table 10 shows the parameter estimates obtained from the analysis of QTcF data. The sponsor's estimate of $QTcF_{BASE}$ (E0 in Table 8) is identical to the estimate of $QTcF_{BASE}$ for the Emax model on vardenafil data only (see Table 10). This likely reflects the abundance of baseline data. The estimate of $QTcF_{MAX}$ is lower (7.95) for the mixed effects Emax model of vardenafil data only than for the sponsor's population PK/PD model of all the data (8.29). This discrepancy is conservative with regards to safety. That is, according to the sponsor's estimate, the drug is less safe than according to the reviewer's estimate. The EC50 estimate for the mixed effects model on vardenafil only data (1.59) is lower than the sponsor's estimate of EC50V (2.44). This discrepancy is anti-conservative with regards to safety. That is, the sponsor's model predicts that it takes a higher concentration to reach half-maximum response than the reviewer's analysis. Given that Emax is lower for the reviewer's analysis, reaching this Emax at a lower concentration is likely less of a concern.

	Linear Model $QTcF = QTcF_{BASE} + Slope*C$		Emax Model $QTcF = QTcF_{BASE} + \frac{QTcF_{MAX}*C}{EC_{50} + C}$	
	Naïve Pooled	Mixed Effects	Naïve Pooled	Mixed Effects
$QTcF_{BASE}$ (se)	389.4 (0.259)	389.1 (1.85)	386.5 (0.359)	386.8 (1.83)
Slope (se)	0.0505 (0.0055)	0.0900 (0.0134)	NA	NA
$QTcF_{MAX}$ (se)	NA	NA	7.54 (0.544)	7.95 (0.308)
EC50 (se)	NA	NA	1.04 (0.459)	1.59 (0.324)

Table 10. Parameter Estimates (Standard Error) for Models of Fridericia Corrected QT Interval Data.

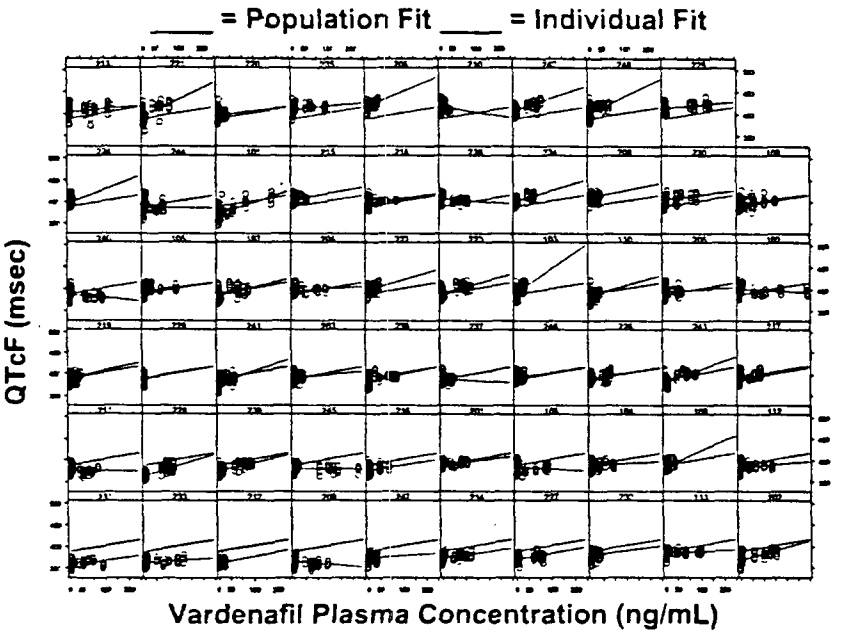


Figure 17. Individual and Population Fit of Reviewer's Mixed Effects Linear Model for Fridericia Corrected QT Interval Data. Model fit to data from 10 mg and 80 mg vardenafil study arms. The line which is the same in all panels represents the population fit.

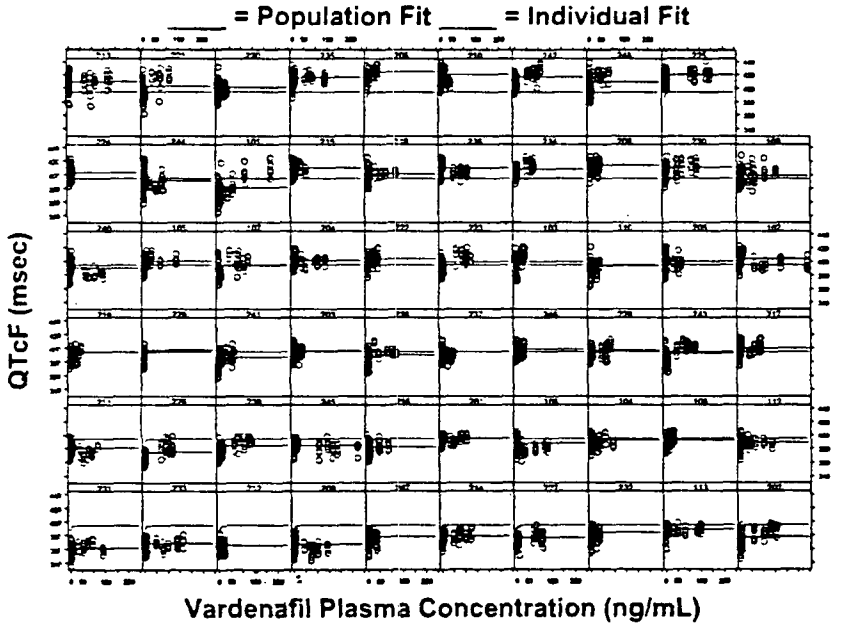


Figure 18. Individual and Population Fit of Reviewer's Mixed Effects Emax Model for Fridericia Corrected QT Interval Data. Model fit to data from 10 mg and 80 mg vardenafil study arms. The line which is the same in all panels represents the population fit.

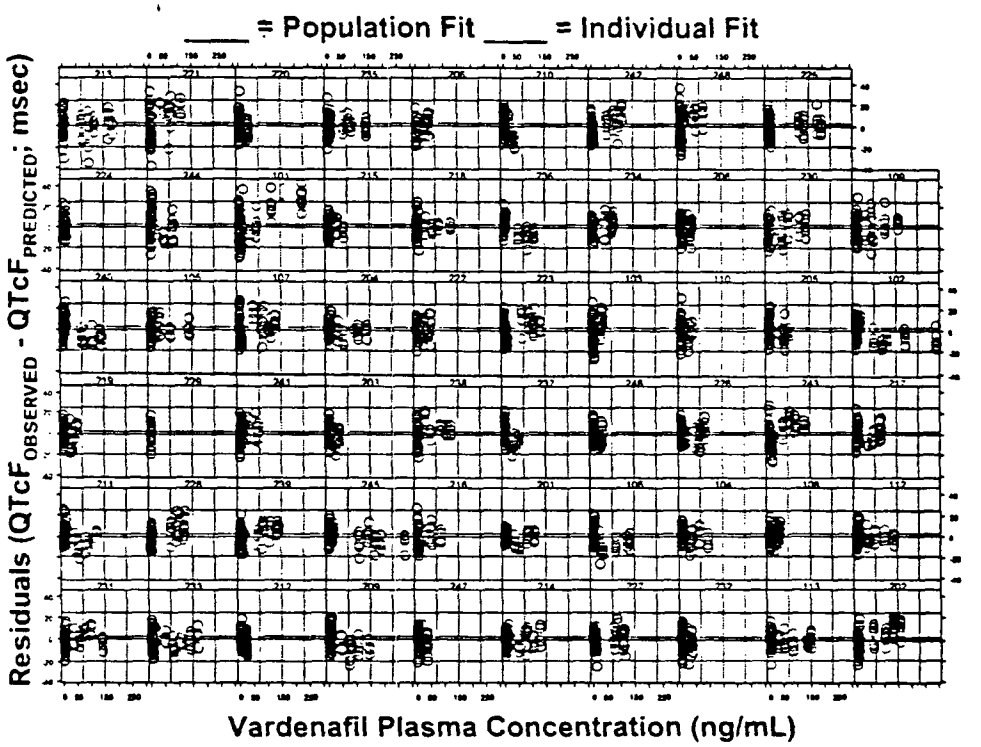


Figure 19. Residual Diagnostic Plot for Reviewer's Mixed Effects Emax Model for QTcF Data.
Model fit to data from 10 mg and 80 mg vardenafil study arms.

Model for QTcI Data

The log likelihood for the QTcI data with respect to the mixed effects linear model versus the mixed effects Emax model was –19559 versus -19734, respectively. The Emax model yielded a significantly better fit to the vardenafil data than the linear model with $p<.05$.

Figure 20 and Figure 21 are plots of the individual and population fit to each subjects' vardenafil data for the linear and Emax mixed effects models, respectively. As with the models for QTcF, it is unclear according to visual inspection whether the Emax model yields any benefit relative to the linear model. Figure 22, the plot of the residuals for the Emax model for each individual, shows uneven scatter around the zero line and an increasing trend between concentration and response for many individuals' data. Reexamination of Figure 20 and Figure 21 suggests that several subjects have not reached $QTcI_{MAX}$ during the course of the study.

Table 11 shows the parameter estimates obtained during the analyses. The estimate of $QTcI_{BASE}$ is similar to the estimate of $QTcF_{BASE}$ in Table 10. As expected from the results reported in the Mean Analysis section of this review, the estimate of $QTcI_{MAX}$ is lower (6.68) than for QTcF (7.95). The EC50 estimate for the mixed effects model of QTcI for vardenafil only data (Table 11: 2.02) is higher than estimated for the QTcF model (Table 10: 1.59) and closer to the sponsor's estimate of EC50V (Tqble 8: 2.44).

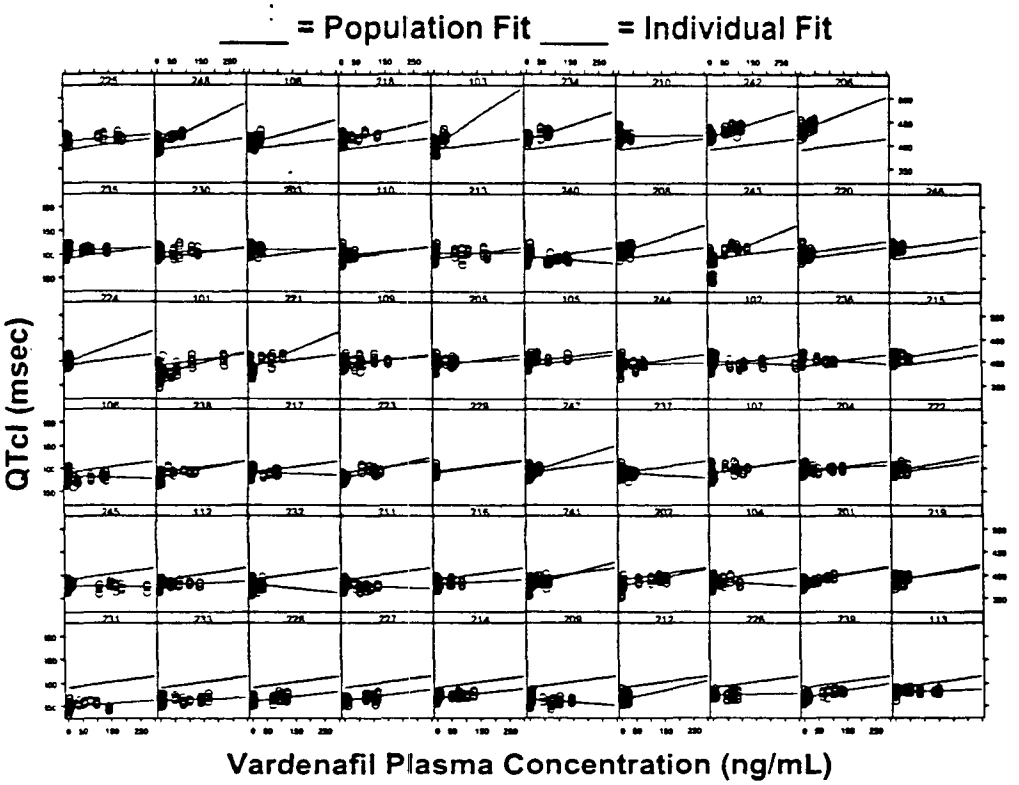


Figure 20. Individual and Population Fit of Linear Model to Individually Corrected QT Interval Data. Model fit to data from 10 mg and 80 mg vardenafil study arms. The line which is the same in all panels represents the population fit.

APPEARS THIS WAY
ON ORIGINAL

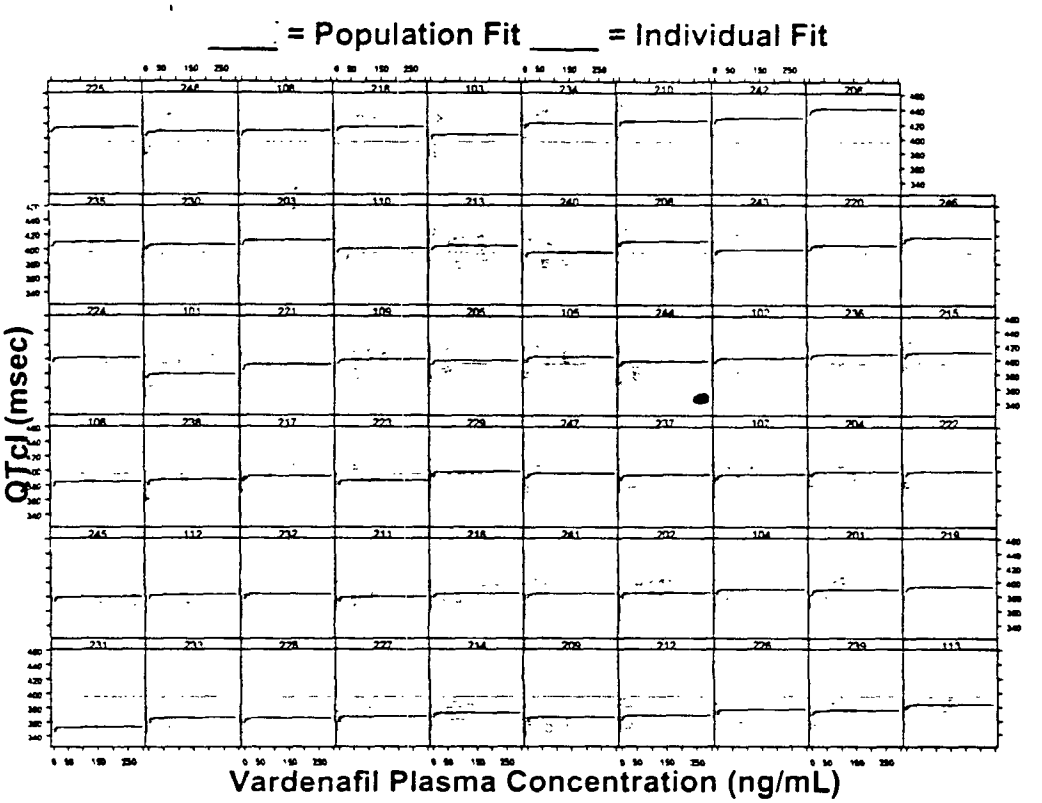


Figure 21. Individual and Population Fit of Emax Model to Individually Corrected QT Interval Data. Model fit to data from 10 mg and 80 mg vardenafil study arms. The line which is the same in all panels represents the population fit.

APPEARS THIS WAY
ON ORIGINAL

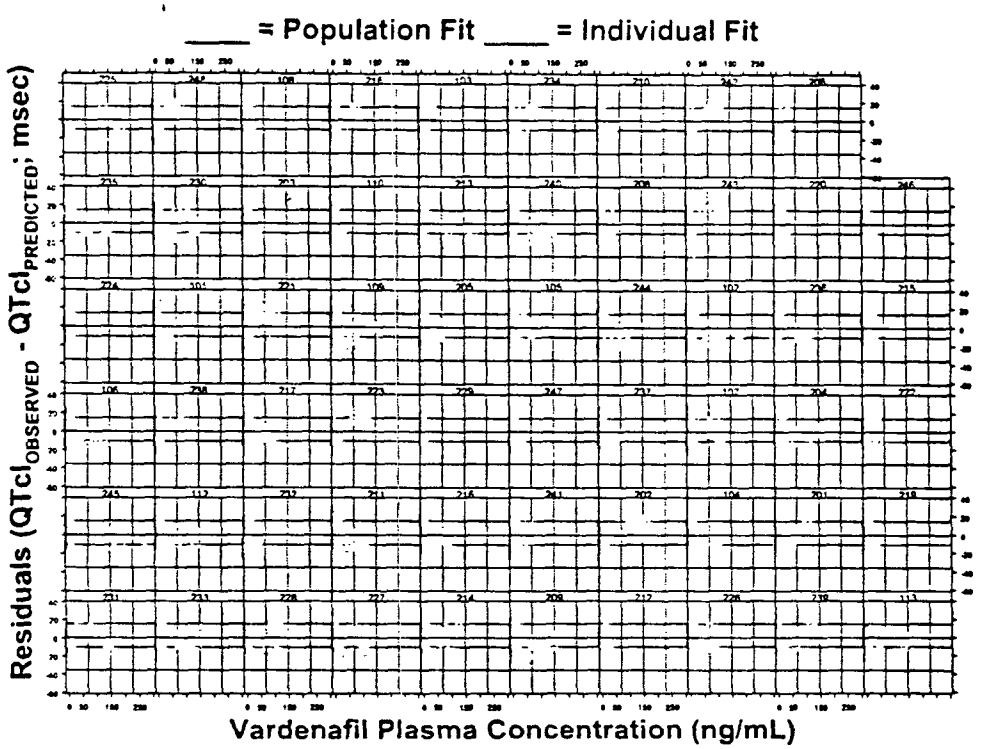


Figure 22. Residual Diagnostic Plot for Reviewer's Mixed Effects Emax Model for QTcI Data. Model fit to data from 10 mg and 80 mg vardenafil study arms.

	Linear Model $QTcI = QTcI_{BASE} + Slope*C$	Emax Model $QTcI = QTcI_{BASE} + \frac{QTcI_{MAX}*C}{EC_{50} + C}$
	Naïve Pooled	Mixed Effects
$QTcI_{BASE}$ (se)	390.7 (2.19)	388.9 (2.21)
Slope (se)	0.083 (0.014)	NA
$QTcI_{MAX}$ (se)	NA	6.68 (0.299)
EC50 (se)	NA	2.02 (0.436)

Table 11. Parameter Estimates (Standard Error) for Models of Individually Corrected QT Interval Data. Model fit to data from 10 mg and 80 mg vardenafil study arms.

Figure 23 is a plot of all of the the vardenafil concentration and response data with the reviewer's mixed effects Emax model population prediction line superimposed in blue. This plot is analogous to the sponsor's plot provided in Figure 15. To put the results in clinical perspective, the orange vertical lines indicate the range of maximum vardenafil concentrations observed (17.5 to 49 ng/mL) after dosing 5 mg vardenafil with 600 mg BID ritonavir. Assuming the Emax model is correct, maximum response appears to be reached on average below or at the bottom of the range of Cmax values obtained when coadministering 5 mg vardenafil with ritonavir. As the individual plots showed, however, many subjects' did not reach QTc max during the course of the study.

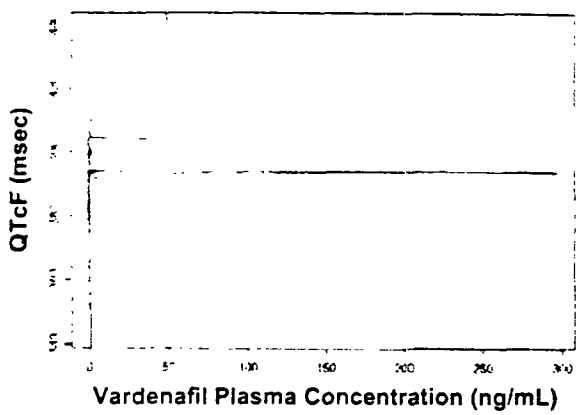


Figure 23. QTcF as a Function of Vardenafil Plasma Concentration for All Subjects. Blue line: population prediction of reviewer's mixed effects Emax model. Orange (vertical) bars: range of maximum vardenafil concentrations observed (17.5 to 49 ng/mL) after dosing 5 mg vardenafil with 600 mg BID Ritonavir.

APPEARS THIS WAY
ON ORIGINAL

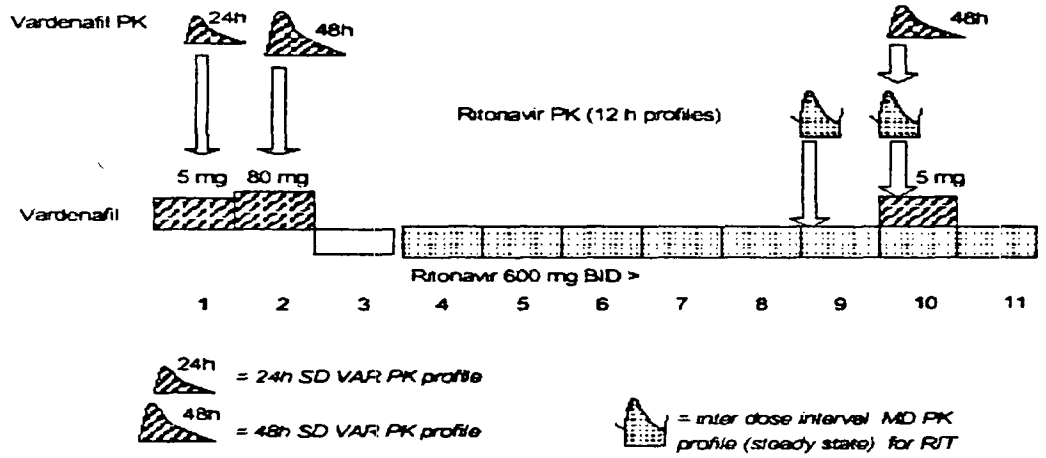
Study 100512 : Effect of Ritonavir on the PK of Vardenafil (and *vice versa*)

Design

This was an open-label and non-randomized study in 18 health subjects ranging in age from 30 to 70 years. The study flowchart is shown in **Figure 1** and is summarized as follows:

Day 1: Vardenafil 5-mg (single dose)
Day 2: Vardenafil 80-mg (single dose)
Day 4: Ritonavir 300-mg BID (two doses)
Day 5: Ritonavir 400-mg BID (two doses)
Day 6-11: Ritonavir 600-mg BID (twelve doses)
Day 10: Vardenafil 5-mg (single dose)
On Days 1, 2 and 10, vardenafil was administered two hours before a light breakfast. On Day 10, vardenafil was administered simultaneously with the morning dose of ritonavir.

On Day 1, serial blood samples were collected for 24 hours after vardenafil administration for determination of vardenafil and vardenafil metabolite (M1) concentrations. After vardenafil administrations on Days 2 and 10, serial blood samples were also collected for 48 hours for the determination of vardenafil and vardenafil metabolite M1 concentrations. In addition, blood samples were collected over 12 hours on Days 9 and 10 for ritonavir PK. Several safety parameters were monitored throughout the study. During the study, subjects were confined to the clinic on Days -1, 1, 2, 3, 7, 8, 9, 10, and 11. On Day 12, approximately 48 hours after the final dose of vardenafil, subjects had an end-of-study full laboratory, followed by a complete physical examination and an ECG. Subjects were then discharged from the clinic on Day 12. Below is a schematic of the study design.



PK Analysis:

The primary PK parameters of interest were $AUC_{0-\infty}$ and Cmax on Days 1 and 10 for vardenafil and AUC_{0-12h}, and Cmax on Days 9 and 10 for ritonavir. Other PK parameters (AUC_{0-24h}, AUC_{0-tn}, Tmax, half-life and mean residence time-MRT) were also calculated as reported. The primary analysis was to compare vardenafil 5-mg alone versus vardenafil 5-mg in combination with ritonavir. The secondary analysis was to compare ritonavir alone versus ritonavir in combination with vardenafil 5-mg. For each comparison, the natural logarithm of the PK variables, except Tmax, were analyzed using analysis of variance (ANOVA) with terms for treatment condition and subject. A 90% two-sided confidence interval for the ratio of geometric LS means of two treatment conditions is presented. In addition, *P* values for testing equality of the means is provided. The vardenafil 80-mg data are tabulated and summarized using descriptive statistics, no formal testing was performed.

Results

Table I. Geometric mean (%CV) vardenafil PK parameters on Day 1 (5-mg administered alone) and on Day 10 (5-mg administered in combination with ritonavir 600 mg BID) and mean ratio and 90 %CI

	Vardenafil 5-mg dosed alone (n = 18)	Vardenafil 5-mg with ritonavir 600-mg BID (n = 18)	Geometric LS mean ratio [90 % CI][b]
C_{max}, µg/L	2.37	30.05	12.69 [9.55 – 16.85]
T_{max}, hr[a]	1.0	2.0	
AUC_{0-24} µg×hr/L	7.11	349.1	49.07 [37.60 – 64.04]
$AUC_{0-\infty}$ µg×hr/L	7.19	778.9	108.3 [86.4 – 135.8]
Half-life, hr	2.64	25.66	9.70 [7.68 – 12.26]
MRT, hr	3.94	37.95	9.63 [7.78 – 11.91]

[a] Median [range]
[b] Vardenafil 5-mg with ritonavir versus vardenafil 5-mg alone
Source: Section 14, Tables 14.2/1.1 and 14.2/2.1.

Table II. Geometric mean (%CV) vardenafil metabolite M1 PK parameters on Day 1 (5-mg administered alone) and on Day 10 (5-mg administered in combination with ritonavir 600 mg BID) and mean ratio and 90 %CI

	Vardenafil 5-mg dosed alone (n = 18)	Vardenafil 5-mg with ritonavir 600-mg BID (n = 18)	Geometric LS mean ratio [90 % CI][b]
C_{max}, µg/L	3.42	0.77	0.20 [0.16 – 0.25]
T_{max}, hr[a]	1.0	2.5	
AUC_{0-24} µg×hr/L	6.73	6.2	0.86 [0.63 – 1.17]
$AUC_{0-\infty}$ µg×hr/L	6.73	7.81 [c]	1.09 [0.65 – 1.83]
Half-life, hr	1.54	6.71 [c]	3.77 [2.05 – 6.92]
MRT, hr	2.22	11.29 [d]	4.68 [2.73 – 8.01]

[a] Median [range]
[b] Vardenafil 5-mg with ritonavir ver... ; vardenafil 5-mg alone
[c] n = 16
[d] n = 13
Source: Section 14, Tables 14.2/1.3 and 14.2/2.2.

Table III. Geometric mean (%CV) vardenafil and vardenafil metabolite M1 PK parameters on Day 2 (80-mg administered alone)

	Vardenafil (n = 18)	Vardenafil metabolite M1 (n = 18)
C_{max}, µg/L	75.47	125.6
T_{max}, hr[a]	0.5	0.5
AUC_{0-24} µg×hr/L	230.1	224.3
$AUC_{0-\infty}$ µg×hr/L	234.9	228.6
Half-life, hr	4.38	6.55
MRT, hr	4.21	3.66

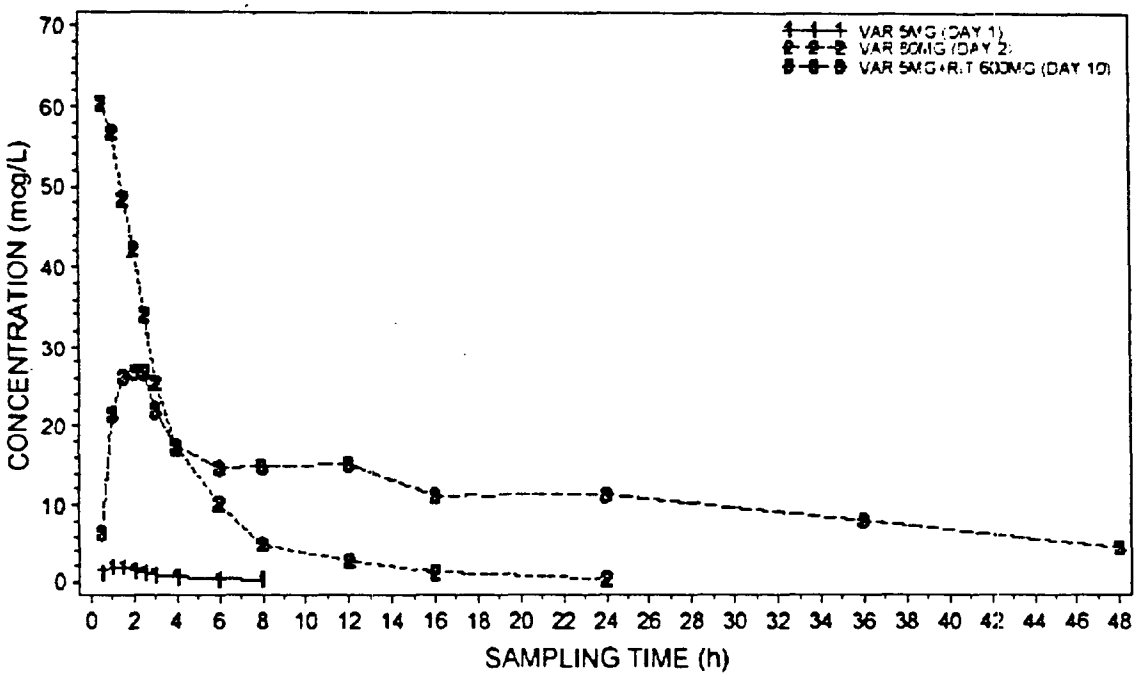
[a] Median [range]
Source: Section 14, Tables 14.2/2.1 and 14.2/2.2.

Table IV. Geometric mean (%CV) ritonavir PK parameters on Day 9 (600-mg dosed alone) and on Day 10 (600-mg dosed in combination with vardenafil 5-mg) and mean ratio and 90 %CI

	Ritonavir 600-mg dosed alone (n = 18)	Ritonavir 600-mg with vardenafil 5-mg (n = 18)	Geometric LS mean ratio [90 % CI][b]
C_{max}, mg/L	18.54	14.47	0.78 [0.65 – 0.93]
T_{max}, hr[a]	2.5	2.5	
AUC_{0-tau} mg×hr/L	102.63	82.6	0.80 [0.70 – 0.93]
$AUC_{0-\infty}$ mg×hr/L	102.63	82.6	0.80 [0.70 – 0.93]

[a] Median [range]
[b] Ritonavir 600-mg with vardenafil 5-mg versus ritonavir 600-mg alone
Source: Section 14, Tables 14.2/1.5 and 14.2/2.3.

Figure I Geometric Mean Vardenafil PK Profile from each arm of the study (Note: This figure is the same as Figure 2 in the previous section on the discussion on QT Prolongation with Study 10929)



APPEARS THIS WAY
ON ORIGINAL

Figure IIA. Individual AUC Following 5 mg Vardenafil Alone (Day 1) and 600 mg Ritonavir (Day 10)

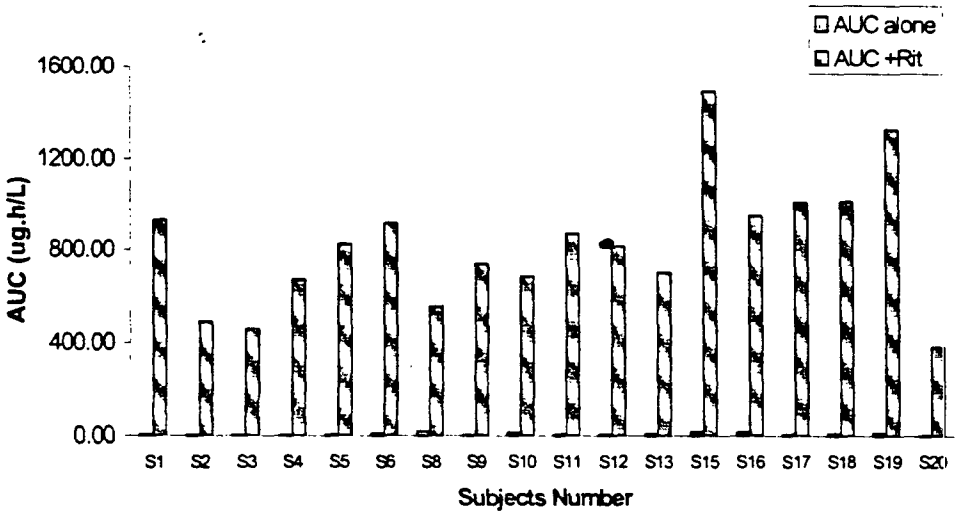


Figure IIB. Individual Fold Increase in Vardenafil AUC With Ritonavir

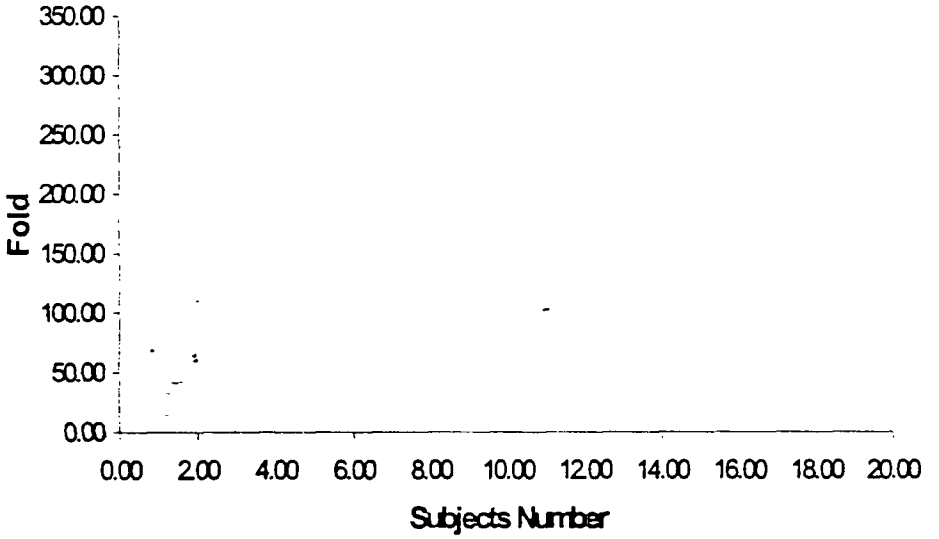


Figure IIIA. Individual Cmax of Vardenafil Alone (Day 1) and in Combination With Ritonavir (Day 10)

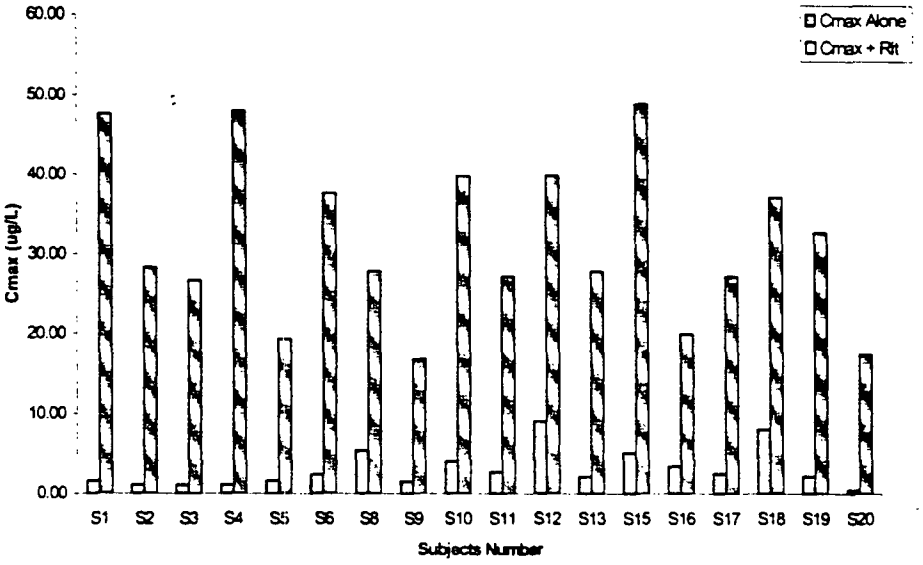


Figure IIIB. Individual Vardenafil Fold Increase in Cmax With Ritonavir (Day 1 vs Day 10)

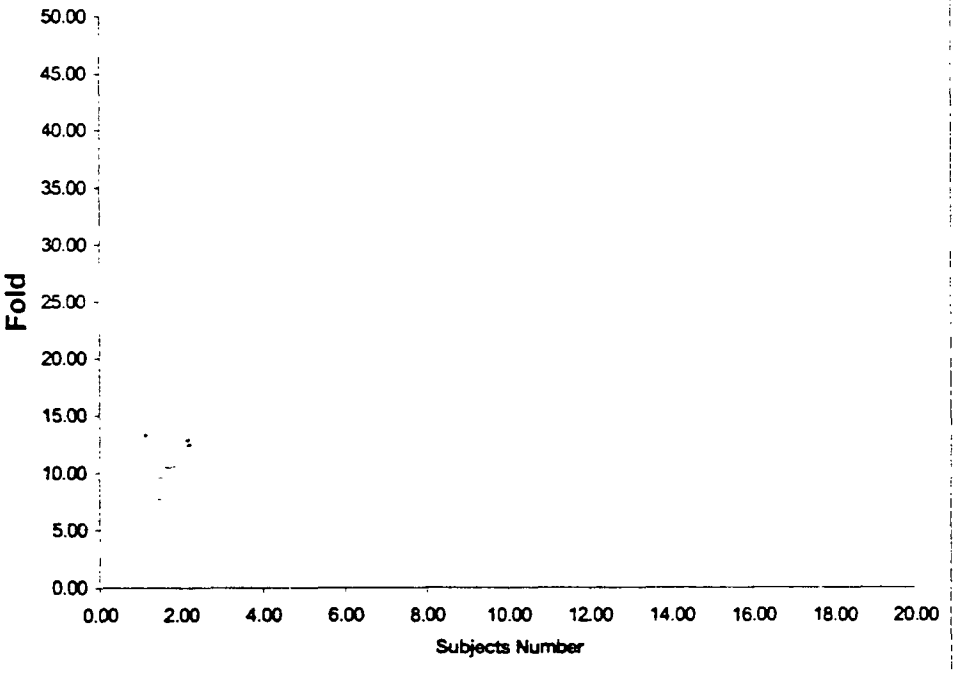


Figure IVA. Vardenafil Half Life When Givben Alone (Day 1) and in Combination With Ritonavir (Day 10)

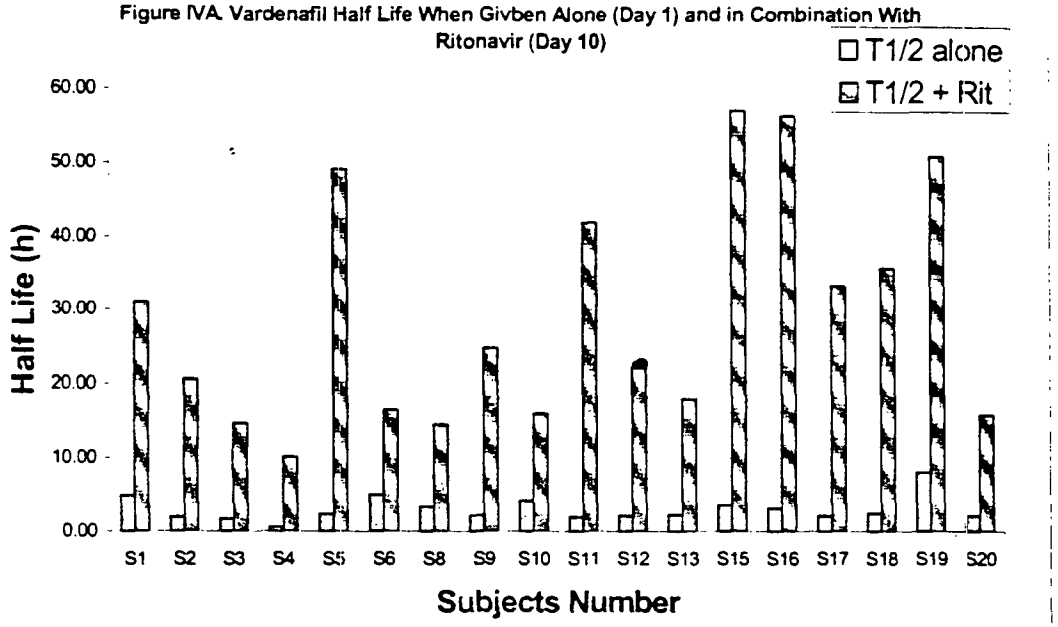
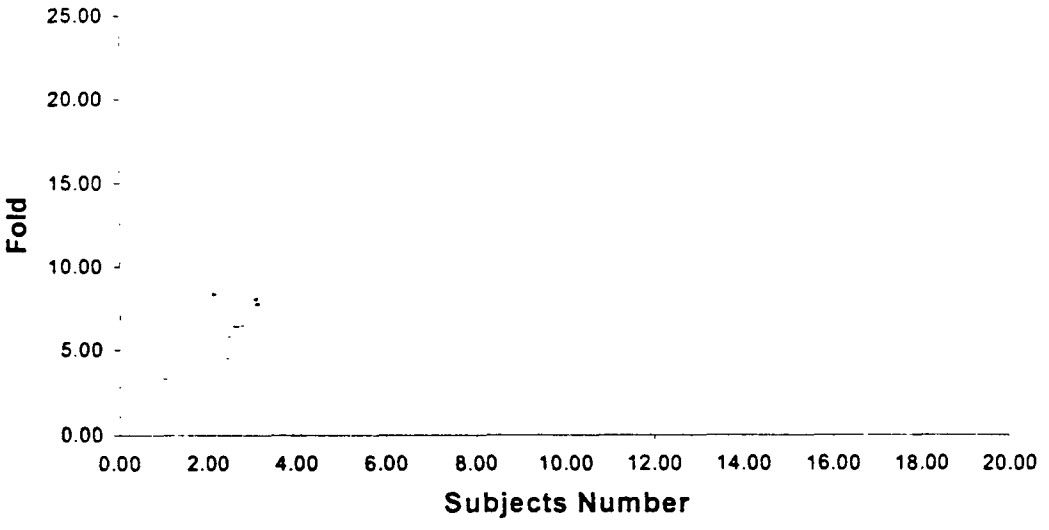


Figure IVB. Vardenafil Fold Increase in Half Life When Given Alone (Day 1) or In Combination with Ritonavir (Day 10)



Reviewer's Comments

- It is clear from the above tables and figures that there is a dramatic effect on inhibition of CYP3A4 by a strong inhibitor (such as ritonavir) on the PK of vardenafil.
- Based on geometric LS mean ratio, a 13-fold increase was observed in vardenafil Cmax and 49-fold increase was observed in vardenafil AUC_{0-24} when 5-mg vardenafil was administered with ritonavir when compared to administration of vardenafil alone. The geometric LS mean ratio (vardenafil + ritonavir versus vardenafil alone) for $AUC_{0-\infty}$ was 108 (fold higher).
- The geometric mean vardenafil half-life was 2.6 hours when given alone and increased nearly 10-fold to 25.7 hours when administered with ritonavir.
- Results indicate that AUC_{0-inf} and C_{max} values for vardenafil in individual patients may be 300 fold and 40 fold higher respectively, when taken with ritonavir. The half life of vardenafil in individual patients may be 10 – 20 fold higher when taken in combination with ritonavir.
- There was approximately a 20% reduction in ritonavir C_{max} and AUC when administered concomitantly with vardenafil 5 mg.
- Based on this reviewer experience, this tremendous level of drug interaction observed in this combination is unique and rare. This may be explained by (a) vardenafil bioavailability is 15%, (b) vardenafil is mostly a specific substrate of CYP3A4 and to some extent, CYP2C9 – ritonavir is a potent inhibitor of CYP3A4 *and* inhibitor of CYP2C9 (thus shutting off both the exit routes for the drug). The extent of change in clearance of vardenafil in the presence of ritonavir is very well evident in the >10 fold increase in vardenafil half-life.
- The above phenomenon of drug interaction is captured by making appropriate dosing recommendation of "not to exceed a 2.5 mg dose of vardenafil in a 72 hour period when in combination with a strong CYP3A4 inhibitor such as ritonavir". It is to be noted that although the frequency of 1 X 2.5 mg dose in 72 hours may wash the drug out prior to the next dose, a single 2.5 mg dose of vardenafil will provide the same exposure (mean) as a 30 mg single dose of vardenafil when in combination with a strong CYP3A4 inhibitor such as ritonavir.

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

---

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

/s/

Dhruba Chatterjee
8/19/03 02:54:36 PM
BIOPHARMACEUTICS

Ameeta Parekh
8/19/03 02:59:50 PM
BIOPHARMACEUTICS
I concur

Leslie Kenna
8/19/03 03:01:37 PM
BIOPHARMACEUTICS
I concur.