CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-400

Statistical Review(s)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION
Clinical Studies

NDA #: 21-400 Amendment

DRUG NAME: Levitra (Vardenafil Hydrochloride) Tablets

INDICATION: Treatment of Erectile Dysfunction

SPONSOR: Bayer Corporation, Pharmaceutical Division

DOCUMENTS REVIEWED:

1. ISS Study report in Electronic form (Submission Date: February 17, 2003)
2. SAS database in EDR

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KEY WORDS: Clinical study, QT interval prolongation safety issue, NDA review

BACKGROUND

Vardenafil is a phosphodiesterase (type 5) inhibitor. Four Phase 3 trials using doses up to 20 mg (5 mg, 10 mg, and 20 mg) vardenafil demonstrated efficacy (measured by Erectile Function Domain of the International Index of Erectile Function and Sexual Encounter Profile Questions 2 and 3). The other drug in this class approved for the treatment of erectile dysfunction is sildenafil (Viagra™). The NDA was received on September 24, 2001, and an "approvable" action taken on July 23, 2002.

This MEMO pertains to a summary of statistical consultations taken place during the NDA amendment review period in response to the July 23, 2002 approvable letter, specifically, the QT interval prolongation issue. The sponsor was requested to address the following clinical deficiencies before the application may be approved: "QT interval prolongation may be a signal for life-threatening cardiac adverse events. Levitra has known drug interactions that significantly increase systemic exposure to the parent drug. Therefore, it is important to rule out QT interval prolongation due to Levitra. Although your application contains results from studies that evaluated the effect of Levitra on the QT interval, this information is insufficient to conclude that Levitra has no significant effect on the QT interval at the approvable doses for marketing and at systemic vardenafil exposures that result from expected drug interactions. More clinical information is needed to ensure that there is no QT prolonging effect. ". The Agency inquired the following information of the sponsor to address this deficiency: "Conduct clinical studies that characterize the vardenafil plasma concentration-response relationship for QTc interval prolongation and that also evaluate the degree of QTc prolongation at plasma concentrations following maximal potential interaction between Levitra and CYP 3A4 inhibitors. These studies must be randomized and double-blinded, and must include a placebo control. An additional active concurrent control group is desirable. The studies must include a sufficient number of patients to provide reliable results. The doses of Levitra to be used must be appropriate to evaluate the degree of QTc interval prologation at therapeutic concentrations, at supratherapeutic concentrations, and at concentrations that follow maximal potential interaction between Levitra and CYP 3A4 inhibitors." In response to the approvable letter, the sponsor submitted the results of Trial 10929.

STUDY DESCRIPTION (Trial 10929)

The primary objective of this study was 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 compared to placebo, as measured by the change from baseline at the 1 hour post-dose time point. The 80 mg dose was chosen because the sponsor believed that maximum plasma concentrations achieved with this dose were above the maximum plasma levels achieved with 5 mg vardenafil (the lowest proposed to-be-marketed dose) and potent CYP 3A4 inhibition (with ritonavir, which increases Cmax by nearly 13 fold). (The to-be-marketed doses of vardenafil are 5, 10, and 20 mg). The one hour time point was chosen because this approximates T_{max}. Secondary objectives were to: 1) characterize the effect of a single 80 mg oral dose of vardenafil on QTc interval compared to placebo, as measured by the change from baseline at the time of maximum concentration (T_{max}), 2) characterize the effect of a single oral dose of 400 mg of moxifloxacin on QTc interval relative to placebo, 3) 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) 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) characterize the pharmacokinetics of vardenafil, sildenafil and moxifloxacin, and 6) explore the relationship between vardenafil, sildenafil and moxifloxacin exposure versus ECG parameters (QTc, QT intervals and HR).

The trial 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), see Table 6 of Sponsor.

Table 6. Regimen description (Sponsor Table)

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.

The study population consisted of healthy adult men between 45 and 60 years of age. Sixty men were enrolled and one man withdrew prior to dosing. Data from 59 subjects are included in the statistical analysis.

Six 12-lead ECGs taken approximately 1 minute apart were obtained at specified times (-0.5, -0.25, predose, 1, 1.5, 2.5, and 4 hours). Conduction intervals from the 12-lead ECGs were manually read and confirmed by an external cardiologist. All ECGs were read blinded. The final conduction intervals entered into the database were those generated by the over-reading cardiologist. 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.

The primary endpoint was the change in Fridericia's correction formula ($QTcF=QT/RR^{1/3}$) from baseline at 1 hour post-dose. QTc at 1 hour post-dose was determined from the average of the 6 replicate measurements taken at 1 hour post-dose and baseline QTc was determined from the average of all 18 pre-dose measurements. Secondary endpoints included change from baseline at the time of maximum concentration (T_{max}), raw QT intervals and heart rate, and 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. Based on median values, T_{max} occurred at approximately 1.2 hour postdose following oral 10 and 80 mg vardenafil. Exploratory endpoints included maximum change from baseline and time averaged change from baseline.

RESULTS

The change in heart rate at one hour post-dose is shown in Table 7 of Sponsor.

Table 7. Change from Baseline in HR (bpm) at 1 hour post-dose (Sponsor's Table)

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.

Point estimates and 90% confidence intervals for change from baseline at 1 hour post-dose for QTc corrected using Fridericia's formula and QTCi are provided in Tables 8 and 9 of Sponsor.

Table 8: Change from baseline in QTcF (msec) at 1 hour post-dose (Sponsor Table)

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.

Table 9: Change from Baseline in QTci (msec) at 1 hour post-dose (Sponsor Table)

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.

The Advisory Committee meeting focused on the following issues:

1) clinical trial designs for assessment of QT prolongation
2) approaches to the correction of QT interval for drugs that increase heart rate
3) risks of cardiac arrythmias associated with different degrees of QT prolongation

REVIEW COMMENTS

Based on the pre-specified statistical analysis plan, viz., QT interval prolongation is to be evaluated at post-dose 1-hour and based on the Fridericia correction, the results showed an increase in QTc (Fridericia) of 8 msec (90% CI: 6-9) and 10 msec (90% CI: 8-11) at 10 and 80 mg doses compared to placebo. Although the sponsor also performed a few analyses including an analysis using QTci individual measurements and showed an increase in QTci of 6 msec (90% CI: 3-6) and 8 msec (90% CI: 4-7) at 10 and 80 mg doses compared to placebo, this was not a pre-specified analysis. As the appropriate analysis method for QT measurements is evolving and one of the major discussion points was on the proper statistical analysis using QT correction methods versus Holter monitoring method during the advisory committee meeting, the methodological developments are ongoing.

From the results of the various analyses, it appeared that the QTcF exceeds the pre-defined threshold of 10 msec for vardenafil 80 mg dose as compared to placebo. The statistically significant longer QTc interval with upper 90% confidence interval of 11 msec was observed. Whether such magnitude of QT interval prolongation is clinically meaningful is deferred to clinical judgment.

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Senior Mathematical Statistician

cc: Marcea Whitaker M.D. (HFD-580), George Benson, M.D. (HFD-580), Donna Griebel, M.D. (HFD-580), Eufrecina Deguia (HFD-580), Sue-Jane Wang, Ph.D. (HFD-715), Mike Welch, Ph.D. (HFD-715), S. Edward Nevius, Ph.D. (HFD-715), Charles Anello, Ph.D. (HFD-700)

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/s/

Sue Jane Wang
8/12/03 02:22:56 PM
BIOMETRICS

Mike Welch
8/12/03 02:31:44 PM
BIOMETRICS
Concur with review.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CLINICAL STUDIES

NDA:	21-400
Name of drug:	Levitra (vardenafil)
Applicant:	Bayer
Indication:	Erectile Dysfunction
Documents reviewed	ISE, Study Reports for trials 100249, 10128, 100250, 100285
Project manager:	Freshnie DeGuia (HFD-580).
Clinical reviewer:	George Benson, M.D. (HFD-580)
Dates:	Received 9/24/01
Statistical reviewer:	David Hoberman, Ph.D. (HFD-715)
Statistics team leader:	Mike Welch, Ph.D. (HFD-715).
Biometrics division director:	S. Edward Nevius, Ph.D. (HFD-715)

Keywords: NDA review, clinical studies, responders analysis

Background

The sponsor has submitted four (4) double-blind, parallel, placebo-controlled, multi-center trials of vardenafil (V) in support of its efficacy and safety for the indication of erectile dysfunction. The table below displays the general features of the 4 trials:

Major Efficacy Trials[a] of Vardenafil

Study # (country)	Duration of treatment	Treatment groups[b]	Number of patients ITT/completers	ED population	Caucasians (%)	Mean age (yr) (range)
100249	26 weeks	Placebo	177/91	General[c]	77	57 (26-76)
(NA)		V 5 mg	190/128		77	58 (29-82)
		V 10 mg	196/151		80	57 (27-83)
		V 20 mg	186/138		82	58 (20-79)
10128	12 weeks	Placebo	160/140	General[c]	68	56 (23-78)
(EU)		V 5 mg	156/146		66	57 (21-78)
		V 10 mg	157/148		68	55 (26-75)
		V 20 mg	163/137		67	56 (25-74)
		S 50 mg	162/147		68	56 (22-81)
100250	12 weeks	Placebo	140/121	Diabetics[c]	79	57 (35-74)
(NA)		V 10 mg	149/131		82	58 (33-81)
		V 20 mg	141/127		78	57 (34-78)
100285	12 weeks	Placebo	137/97	Post-pros-	93	60 (47-72)
(NA)		V 10 mg	139/114	tatectomy	99	61 (44-77)
		V 20 mg	147/119		87	60 (45-74)

[a]Randomized, double-blind, placebo-controlled, parallel-group, multicenter trials
[b]S = sildenafil; V = vardenafil; ITT = intent to treat
[c]Excluded patients with radical prostatectomy
[d]Race was not reported in 27% to 29% of patients (French patients) because racial/ethnic information may not be collected in France

Sponsor's Results

The primary efficacy outcomes were the Erectile Function domain of the IIEF, and the following two questions from the patients diary: 1) "Were you able to insert your penis into the partner's vagina?" and 2) "Did your erection last long enough for you to have successful intercourse?". The sponsor's tables below display the results for the primary endpoints in each trial.

: Study 100249—Results[a] for Primary Efficacy Parameters: IIEF EF Domain, Success in Penetration, and Maintenance of Erection (ITT Population)

Variable	Placebo	Vardenafil 5 mg	Vardenafil 10 mg	Vardenafil 20 mg	
IIEF domain: EF at Week 12 LOCF					
N	170	188	195	183	
LS mean baseline	13.6	12.5	13.4	12.8	
LS mean value (SE)	15.0 (0.7)	18.4 (0.6)	20.6 (0.6)	21.4	(0.6)
		P<0.0001	*P*<0.0001	*P*<0.0001	
Week 12 overall per-patient diary: success in penetration (% yes)					
N	171	189	194	182	
LS mean baseline	46.0	42.8	45.4	40.9	
LS mean value (SE)	51.7 (2.5)	65.5 (2.4)	75.5 (2.4)	80.5	(2.5)
		P<0.0001	*P*<0.0001	*P*<0.0001	
Week 12 overall per-patient diary: maintenance of erection for successful intercourse (% yes)					
N	171	188	194	182	
LS mean baseline	14.9	14.0	14.6	14.7	
LS mean value (SE)	32.2 (2.7)	50.6 (2.6)	64.5 (2.6)	64.5	(2.7)
		P<0.0001	*P*<0.0001	*P*<0.0001	

Source: Tables 14.2/1.1 and 14.2/1.2, Study 100249
[a]The *P* value is for the comparison of the vardenafil groups with placebo

Study 10128 Results[a] for Primary Efficacy Parameters: IIEF EF Domain, Success in Penetration, and Maintenance of Erection (ITT Population)

Variable	Placebo	Vardenafil 5 mg	Vardenafil 10 mg	Vardenafil 20 mg	Sildenafil 50 mg
IIEF domain: EF at Week 12 LOCF					
N	158	150	155	158	156
LS mean baseline	13.01	13.19	13.05	13.25	13.33
LS mean value (SE)	13.23 (0.62)	19.76 (0.63)	20.91 (0.62)	21.49 (0.62)	21.27 (0.62)
		P<0.0001	*P*<0.0001	*P*<0.0001	*P*<0.0001
Week 12 overall per-patient diary: success in penetration (%)					
N	152	152	151	156	156
LS mean baseline	41.72	47.80	43.92	43.77	45.81
LS mean value (SE)	45.35 (2.57)	71.75 (2.56)	76.43 (2.56)	79.48 (2.54)	78.74 (2.54)
		P<0.0001	*P*<0.0001	*P*<0.0001	
Week 12 overall per-patient diary: maintenance of erection for successful intercourse (%)					
N	151	152	151	156	156
LS mean baseline	15.91	14.60	15.95	15.31	16.59
LS mean value (SE)	24.95 (2.92)	54.88 (2.89)	61.58 (2.90)	63.92 (2.87)	64.93 (2.87)
		P<0.0001	*P*<0.0001	*P*<0.0001	*P*<0.0001

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

Study 100250—Results[a] for Primary Efficacy Parameters: IIEF EF Domain at LOCF and Overall Per-Patient Diary Results for Penetration and Maintenance Questions (ITT Population)

	Placebo	Vardenafil 10 mg	Vardenafil 20 mg
IIEF domain: erectile function at LOCF			
LS mean baseline	11.2	11.0	12.4
LS mean value (SE)	12.6 (0.7)	17.1 (0.7)	19.0 (0.7)
		P = 0.0001	*P* = 0.0001
Overall per-patient diary: success in penetration (% yes)			
LS mean baseline	33.2	30.9	41.1
LS mean value (SE)	36.4 (2.8)	61.2 (2.8)	63.8 (2.8)
		P = 0.0001	*P* = 0.0001
Overall per-patient diary: maintenance of erection for successful intercourse (% yes)			
LS mean baseline	11.3	9.4	15.4
LS mean value (SE)	23.0 (3.1)	49.2 (3.1)	54.2 (3.1)
		P = 0.0001	*P* = 0.0001

Source: Tables 14.2/1.1 and 14.2/1.2, Study 100250
[a] *P* value is for comparison of the vardenafil groups with placebo

Study 100285—Results[a] of IIEF EF Domain at LOCF and Overall Per-Patient Diary Results for Penetration and Maintenance Questions (ITT Population)

	Placebo	Vardenafil 10 mg	Vardenafil 20 mg
IIEF domain: EF at LOCF			
N	135	135	143
LS mean baseline	9.1	9.3	9.2
LS mean value (SE)	9.2 (0.7)	15.3 (0.7)	15.3 (0.7)
		P = 0.0001	P = 0.0001
Overall per-patient diary: success in penetration (% yes)			
N	135	134	142
LS mean baseline	14.2	21.0	18.3
LS mean value (SE)	21.8 (3.4)	46.6 (3.4)	47.5 (3.4)
		P = 0.0001	P = 0.0001
Overall per-patient diary: maintenance of erection for successful intercourse (% yes)			
N	135	134	142
LS mean baseline	6.0	6.6	7.0
LS mean value (SE)	9.9 (3.3)	37.2 (3.3)	34.2 (3.3)
		P = 0.0001	P = 0.0001

Source: Tables 14.2/1.1 and 14.2/1.2, Study 100285
[a] The *P* value is for the comparison of the vardenafil groups with placebo

It is clear that all doses of vardenafil were statistically superior to placebo in all 4 trials. There are no technical statistical issues which need to be addressed in this review since there are no realistic issues concerning Type I error or bias.

Dose Response

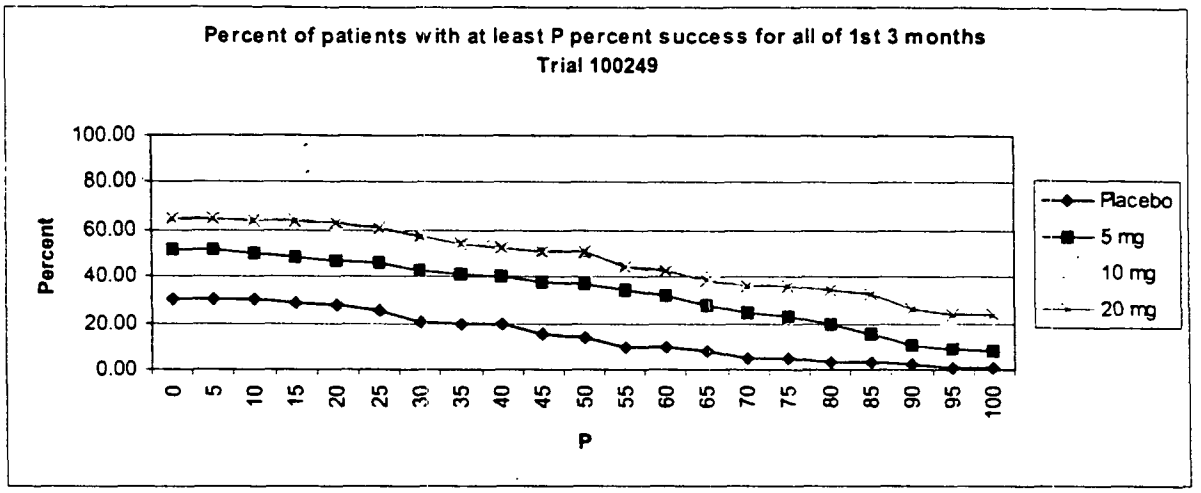
The table below displays the sponsor's dose to dose comparisons in study **100249** showing that there is no statistically significant difference between 10mg and 20 mg. However, 10 mg is statistically superior to 5 mg.

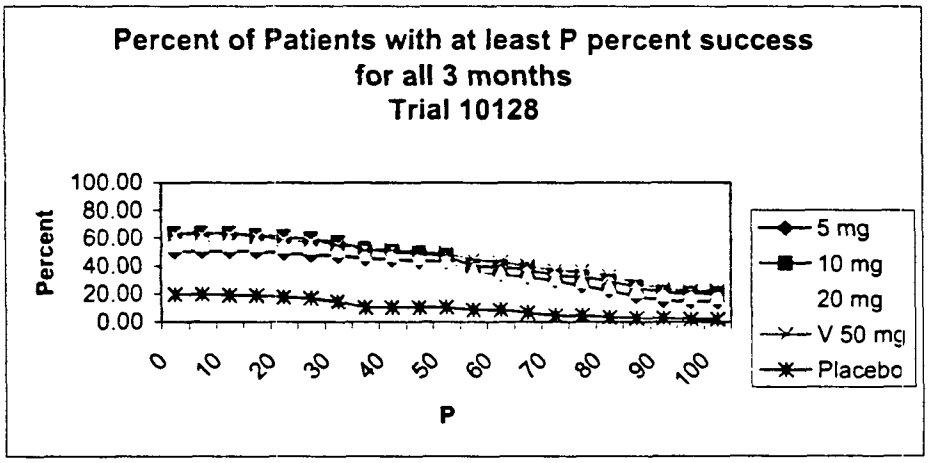
Study 100249 95% Confidence Intervals for the Differences Between Vardenafil Dose Groups LS Means for the Primary Efficacy Analysis at Week 12 (ITT Population)

LS mean difference		95% Confidence interval Lower limit	Upper limit	*P* value
IIEF domain: EF at LOCF				
Vardenafil 10 mg 5 mg	2.2	0.6	3.8	0.0058
Vardenafil 20 mg 5 mg	3.0	1.4	4.6	0.0002
Vardenafil 20 mg 10 mg	0.8	-0.8	2.4	0.3083
Overall per-patient diary: success in penetration (% yes)				
Vardenafil 10 mg 5 mg	10.0	4.1	16.0	0.0010
Vardenafil 20 mg 5 mg	15.0	8.9	21.1	<0.0001
Vardenafil 20 mg 10 mg	5.0	-1.1	11.0	0.1059
Overall per-patient diary: maintenance of erection for successful intercourse (% yes)				
Vardenafil 10 mg 5 mg	13.9	7.5	20.3	<0.0001
Vardenafil 20 mg 5 mg	14.0	7.4	20.5	<0.0001
Vardenafil 20 mg 10 mg	0.04	-6.5	6.5	0.9899

The sponsor indicates that there was a statistically significant difference between 10mg and 20 mg in study **100250 (in diabetics)** on the two diary questions. However, there is no evidence of superior efficacy of 20mg in study **100285 (in radical prostatectomy patients)**.

The sponsor's results tabled above evaluate only a cross section in time (the last week of the trial) and so does not address the issue of longitudinal success rates for individual subjects. This reviewer has computed, for each trial, the percentage of patients who had at least 'P' percent success on the question: "Did your erection last long enough for you to have successful intercourse?" *for all 3 months of the trial* (the 1st 3 months in the case of trial 100249). The plots on the next pages display these percentages of long time responders in each group as a function of P on the horizontal axis. For example, in trial 100249, about 50% of the subjects in the 10 mg and 20 mg dose groups had at least 50% success for all of the first 3 months, whereas the percentages were 37% and 14% for the 5 mg group and the placebo group, respectively. These are the percentages on the plot above the number '50' on the horizontal axis.


Percent of patients with at least P percent success for all of 1st 3 months
Trial 100249
Percent
100.00
80.00
60.00
40.00
20.00
0.00
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
P
Placebo
5 mg
10 mg
20 mg


Percent of Patients with at least P percent success
for all 3 months
Trial 10128
Percent
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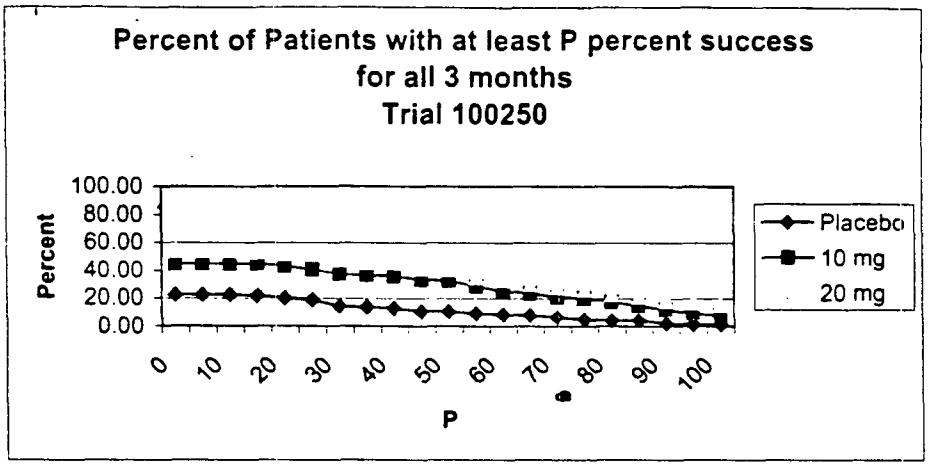
Percent of Patients with at least P percent success
for all 3 months
Trial 100250
Percent
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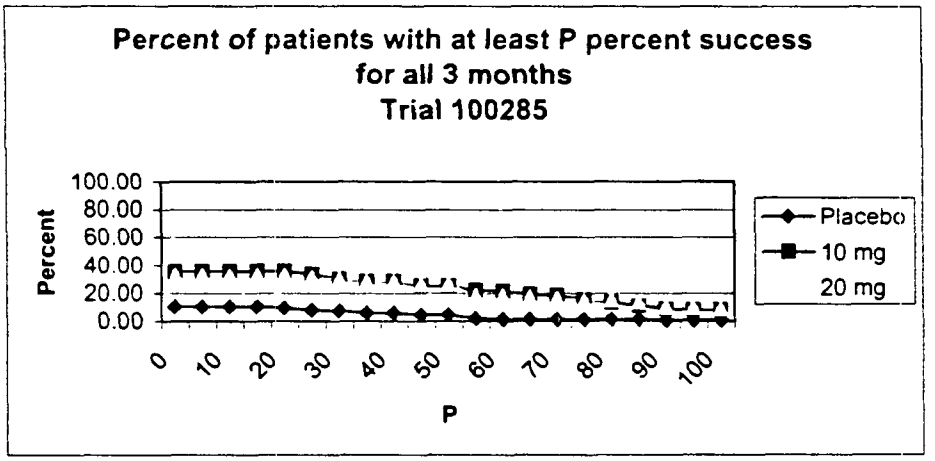
Percent of patients with at least P percent success
for all 3 months
Trial 100285
Percent
100.00
80.00
60.00
40.00
20.00
0.00
0
10
20
30
40
50
60
70
80
90
100
P
Placebo
10 mg
20 mg

Note that the sponsor's statistical comparisons of 10mg and 20 mg during the last week of the studies are consistent with this graphical approach to the longitudinal results. In study **100250**, it does appear that there is a slight advantage to 20 mg, and in study **100285**, there is no evidence at all that 20mg is superior to 10 mg.

Conclusions

The sponsor's four trials provide evidence that all three doses (5 mg 10 mg, and 20 mg) vardenafil are statistically significantly superior to placebo for the treatment of erectile dysfunction. There is no compelling evidence that 20 mg is more efficacious than 10 mg in the general population. The absolute probability of consistent success using vardenfil appears to be less for patients with diabetes or patients who have undergone radical prostatectomy than patients in the general population. (Compare the 4 figures above).

/S/

David Hoberman, Ph.D.
Mathematical Statistician

Concur: Dr. Welch

Dr. Nevius

cc:
Arch NDA# 21-400
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Mike Welch
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