CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-368

MEDICAL REVIEW

Medical Officer's Review of NDA 21-368
Ophthalmology Consultation

NDA 21-368		**Submission dates:**	5/27/03 & 7/22/03
Ophthalmology Consult #2		**Review date:**	10/9/03
IND 54,553			

Sponsor:	Lilly Icos LLC 1209 Orange Street Wilmington, DE 19801 (317) 277-3799
Contact:	Gregory T. Brophy, Ph.D. Director, US Regulatory Affairs Lilly Research Laboratories Indianapolis, IN 46285 Alternate Contact: Catherine A. Melfi, PhD (317) 277-2905
Drug Product:	Cialis (tadalafil tablets) 10 & 20 mg oral IC351 (LY450190)
Pharmacologic Category:	PDE 5 Inhibitor
Proposed Indication:	Erectile dysfunction

Background:

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

Reviewed: Electronic Submission
- Clinical Studies
  - H6D-EW-LVFF
- Proposed package insert labeling
- Integrated Summary of Safety

Note: Clinical studies H6D-EW-LVAN and H6D-EW-LVCN were reviewed in Ophthalmology Consult #1.

Executive Summary

I. Recommendations

A. Recommendation on Approvability

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

B. Recommendation on Phase 4 Studies and Risk Management Steps

Additional adequate and well-controlled studies are recommended to better quantitative the effect of tadalafil on color vision and retinal physiology (as measured by ERG testing). In particular, testing after repeated dosing should be performed.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Three clinical studies evaluating vision were performed with tadalafil. The three studies are so flawed by their execution and analysis that it is not possible to quantitate the effect of tadalafil on vision.

Flaws in Protocol H6D-EW-LVFF include:

- Failure to follow protocol and evaluate eyes independently in the Farnsworth-Munsell test

Flaws in Protocol H6D-EW-LVAN include:

- Failure to record to position of the errors in the Farnsworth-Munsell test.
- Inconsistent visual acuity scores even without tadalafil treatment (may reflect inconsistent refractive correction).
- Ocular motility and cover test inconsistencies even without tadalafil treatment
- Visual acuity scores which are not physiologic.
- Failure to perform scheduled ERG testing on 4 of 18 patients at hour 7
- Failure to perform scheduled ERG testing in most patients at hour 26.

Flaws in Protocol H6D-EW-LVCN include:

- Failure to analyze the results of the Farnsworth-Munsell test according to the protocol plan.
- Failure to show that the positive control had positive findings.
- Reporting of test results as normal or abnormal when the test result is a numerical value and failing to include the value of the test result.

B. Efficacy

Not evaluated in this review.

C. Safety

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

Vision Studies

Title: A Placebo-Controlled, Randomized, Three-Period, Cross-Over Study to Assess the Effects of 40 mg IC351 (LY450190) and 200 mg Sildenafil on Visual Function in Healthy Male Subjects (Protocol H6D-EW-LVFF)

Investigator: [redacted]

Study Centre: [redacted]

Dates of Study: 12 September 2002 through 11 December 2002.

Clinical Phase: Phase 1

Primary Objective: To assess, in healthy male subjects, the effects of 40 mg IC351 and 200 mg sildenafil after a single oral dose on color vision as determined by the FM-100 Hue test.

Study Design

Single center, double-blind, randomized, placebo-controlled, 3-period cross-over study to be performed on 18 healthy male subjects (18-45 years of age). Subjects were to be dosed with 40 mg IC351, 200 mg sildenafil or placebo on Day 1 in each treatment period, such that they received one dose of each of the three treatments.

Number of Subjects:

A total of 63 subjects entered and 59 subjects completed the study in accordance with the protocol, protocol amendment (a), and the treatment randomization. Three subjects were withdrawn: two due to protocol violations (under dosing), and one due to an adverse event (orthostatic hypotension) prior to dosing in Treatment Period 3 that was not considered to be drug-related. One subject was misdosed, receiving two doses of sildenafil but no dose of IC351.

Study Plan	Screening	Treatment Periods 1, 2 and 3		Post-Treatment (within 3 to 5 days)
Activity	Within 14 days before first dose	Day -1	Days 1	
Medical History	X			
Physical Exam	X	X		X
Weight	X			X
Vital Signs	X		Predose and 2 hour postdose	X
ECG	X			X
Laboratory Tests	X	X	X[c]	X
Hepatitis Tests	X			
HIV Test	X			
Drug Screening	X	X		
Ethanol Test	X	X		
Dosing			X (t=0)	
Color Vision (Ishihara)	X			
Visual Acuity	X		X[b]	
Visual Field		X[a]	X[b]	
Intraocular Pressure		X[a]	X[b]	
FM 100-Hue Color Vision		X[a]	1 and 2 hour postdose	
Funduscopy		X[a]	X[b]	
ERG		X[a]	X[b]	
[a] Treatment Period 1 only				
[b] 2 hours post dose				
[c] 24 hours post dose				

Pharmacodynamic Methods

An Ishihara plates test for colour vision was performed at screening only.

The following tests of visual function were performed at specific times during the study. Where these tests were performed at similar times, they were performed in the order shown below:

FM (Farnsworth-Munsell) 100-hue test for colour vision. The total number of errors was tabulated as well as a graphical representation of errors (position and significance). The test was to be carried out for each eye separately

Visual Fields (perimetry): assessment of normality and measurement of deficit (dB) in both eyes.

Distance vision (Snellen test), near vision (according to Keeler) and visual co-ordination (cover test, ocular motility and pupil reaction).

Examination of anterior segments (slit lamp ————) and posterior segments (lens of — of the eye.

Intraocular pressure.

ERG: Flash Ganzfeld full-field ERGs were recorded for both eyes in accordance with the recommendations of the International Society for Clinical Electrophysiology of Vision (Marmor and Zrenner 1995).

Reviewer Comments: *The FM was to have been tested for each eye separately. A binocular test was performed instead. This is a fatal flaw for this test. The results are therefore not interpretable.*

Results:

FM 100-Hue Test:

Reviewer's Comments: *Not interpretable as a result of test being performed binocularly.*

Statistical Analysis of the ERG Latency Times

		LS mean latency time (ms)			Mean difference (95% confidence limits) (ms)	
Light	Eye	IC351	Placebo	Sildenafil	IC351-placebo	IC351-sildenafil
White	L	26.1	25.8	26.5	**0.246 (0.0308, 0.461)**	**-0.491 (-0.710, -0.271)**
A	R	26.4	26.1	27	**0.247 (0.0102, 0.483)**	**-0.593 (-0.833, -0.354)**
White	L	50.2	49.2	51.6	1.01 (-0.232, 2.25)	**-1.36 (-2.62, -0.0974)**
b	R	50.3	49.9	51.7	0.424 (-0.398, 1.25)	**-1.33 (-2.17, -0.498)**
Red	L	25.3	25.3	27.4	-0.0101 (-1.70, 1.68)	**-2.11 (-3.84, -0.379)**
a1	R	25.6	26	26.6	-0.398 (-1.26, 0.460)	**-0.960 (-1.84, -0.0799)**
Red	L	43.3	43.7	46.7	-0.464 (-2.72, 1.79)	**-3.42 (-5.74, -1.11)**
b1	R	44.3	44	46.8	0.286 (-0.800, 1.37)	**-2.50 (-3.62, -1.39)**
Blue	L	105	105	105	-0.403 (-4.27, 3.46)	-0.239 (-4.22, 3.74)
b2	R	105	104	106	0.812 (-3.83, 5.45)	-0.355 (-5.08, 4.38)
30Hz	L	19.9	19.9	23.2	0.00367 (-1.48, 1.49)	**-3.32 (-4.87, -1.78)**
a	R	20.7	21.3	21.7	-0.591 (-2.68, 1.50)	-1.06 (-3.22, 1.10)
30Hz	L	33.7	34.1	37.2	-0.413 (-2.15, 1.32)	**-3.48 (-5.28, -1.68)**
b	R	34.6	35.1	36.2	-0.449 (-2.64, 1.74)	-1.56 (-3.82, 0.708)

Reviewer's Comments: *The ERG is affected by IC351. The white light a-wave latency is lengthened.*

Visual Acuity

		Left eye		Right eye	
Treatment		**Screening**	**2 h**	**Screening**	**2 h**
40 mg IC351	Mean	5.5	5.6	5.6	5.8
	SD	1.21	1.13	1.21	1.83
	Median	5.0	5.0	5.0	5.0
	Min				
	Max				
	N	60	59	60	59
200 mg sildenafil	Mean	5.5	5.6	5.6	5.6
	SD	1.21	1.13	1.21	1.61
	Median	5.0	5.0	5.0	5.0
	Min				
	Max				
	N	60	60	60	60
Placebo	Mean	5.5	5.5	5.6	5.7
	SD	1.21	1.04	1.21	1.48
	Median	5.0	5.0	5.0	5.0
	Min				
	Max				
	N	60	59	60	59

Reviewer's Comments: *There is no significant difference in visual acuity between groups.*

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Update of Ocular Adverse Events

No new patients with color-vision changes during treatment with tadalafil have been identified in the current database.

Three patients whose treatment with tadalafil was associated with color-vision changes were previously reported in the ISS of the original NDA.

One healthy subject in the clinical pharmacology Study LVCN (Subject 48, 20 mg tadalafil) reported a single episode of chromatopsia (reported as blue vision) without abnormality in the Farnsworth-Munsell (FM)-100 Hue test.

Patient 212-6207 in the Phase 3 Study LVBN who had previously experienced a blue tinge to vision consistently after each dose while being treated with sildenafil, reported "visual field defect," described as visual color disturbance with red objects appearing blue and blue and yellow objects appearing orange following the 40th dose of 10 mg tadalafil; this subject took 13 more doses without chromatopsia occurring.

A participant in the open-label Study LVBL reported blue vision (Patient 422-1361, 20 mg tadalafil). Using the MedDRA dictionary, this patient has the preferred term "cyanopsia," which is classified HLGT *vision disorders* and system organ class *eye disorders*.

Postmarketing Events:

There was 1 case report where the primary reaction was categorized in this SOC. This case is summarized in Appendix 3 in the "eye disorders" section of the CIOMS II line listing. In total, there have been 10 reactions categorized in the "eye disorders" SOC. Of these 10 reactions, none were classified as serious and 10 were classified as nonserious (8 unlisted and 2 listed). The unlisted reactions included: *conjunctivitis* (1), *eye pruritis* (1), *eye redness* (3), *asthenopia* (1), and *vision blurred* (2). The listed reactions were: *eye pain* (1) and *eyelid oedema* (1). The reactions, *conjunctivitis* and *eye redness* were noted in this category. Both of these reactions are very similar to conjunctival hyperemia which is already included in the undesirable effects of the CCDS.

Reviewer's Comments: *No changes from original review. Post-marketing events from other countries where the product is approved and marketed are consistent with the proposed labeling as amended in this review.*

17 page(s) of revised draft labeling has been redacted from this portion of the review.

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/s/

Wiley Chambers
10/16/03 04:26:29 PM
MEDICAL OFFICER

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Consultative Clinical Review

NDA: 21-368 (Cialis; tadalafil)

Sponsor: Lilly ICOS

Submission: Definitive QT protocol LVFB

Review date: 7 July 2003

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

Concurrence: Douglas C. Throckmorton, M.D., Division Director

Distribution: NDA 21-368

HFD-580/Spell-LeSane

HFD-580/Hirsch

The maximum dose of tadalafil for which approval is being considered is 20 mg, not more than once per day. Plasma levels of the parent drug peak 2-4 hours or so after dosing. Peak plasma levels of the principal metabolite, methylglucuronide, are said to peak at about 24 hours. Tadalafil is said to have a half-life of about 18 hours. The pharmacokinetics of tadalafil are linear up to about 20 mg, but they are distinctly less than linear at higher doses, so that at 500 mg, the highest dose for which data are available, Cmax is only about 3-fold higher than observed at 20 mg. Tadalafil is a substrate for 3A4, but plasma levels rise modestly with 3A4 inhibition. (See review of study LVEV below.)

The sponsor was unable to allay concerns about potential QT effects on the basis of previous studies conducted without an assay-validating control. At this time, the Division of Cardio-Renal Drug Products is asked to review the results of two clinical studies, LVEV and LVFB.

Study LVEV, entitled "A Study to Assess the Effect of Ritonavir and Ketoconazole on the Pharmacokinetics of 20 mg IC351 in Healthy Subjects", is described in a study report dated 13 February 2003. Study enrollment was between 30 August 2002 and 12 October 2002. The description of the protocol is based on the final protocol, dated 2 August 2002; there were no amendments after the start of enrollment.

Subjects were to be 28 healthy adult males. There were two separate phases, both open-label. In part A, subjects received single oral doses of tadalafil 20 mg alone and then in association with ritonavir 200 or 600 mg twice daily for 10 days. In part B, subjects received tadalafil 20 mg alone and then in association with ketoconazole 400 mg once daily for 10 days. The second doses of tadalafil occurred on day 3 of dosing for ritonavir and ketoconazole. Study data including pharmacokinetic sampling and 12-lead ECGs. Eight subjects were to be enrolled for each of the two ritonavir doses and 12 subjects were to be enrolled for ketoconazole.

Subjects in the ritonavir study were males age 19 to 54. Subjects in the ketoconazole study were males age 20 to 50. All but 3 were Caucasian. Only 3 of 8 subjects receiving the high-dose ritonavir completed study. All subjects on low-dose ritonavir and all but

one subject on ketoconazole completed. None of the withdrawals had any apparent association with electrophysiological effects.

Ritonavir increased the AUC for tadalafil, but had little effect on Cmax, as shown in Figure 1.

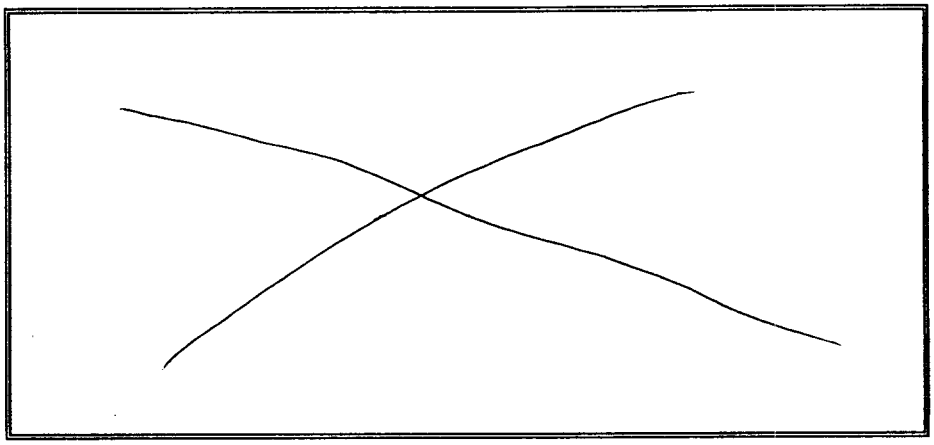

Figure 1. Plasma levels of tadalafil alone and during administration of ritonavir

From page 35 of sponsor's study report.

In contrast, exposure to the principal metabolite of tadalafil was decreased during dosing with ritonavir.

Both Cmax and AUC for tadalafil were increased by treatment with ketoconazole, and exposure to the principal metabolite was decreased by ketoconazole, as shown in Figure 2.

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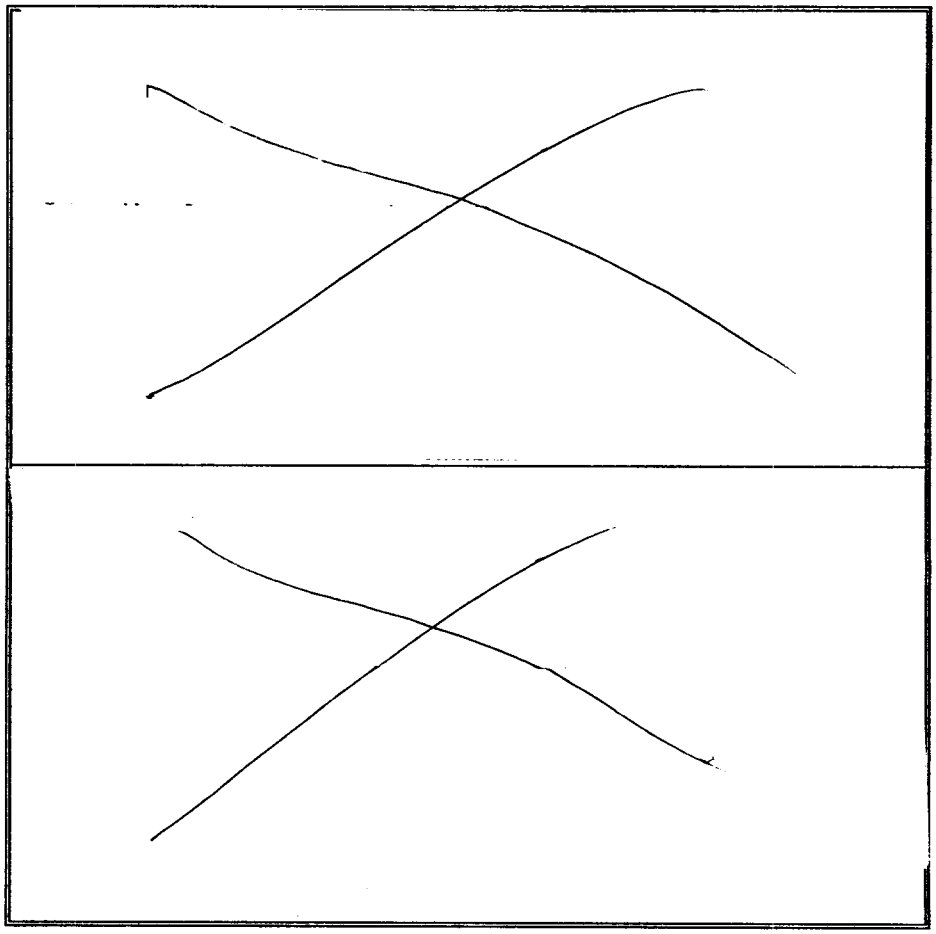


Figure 2. Tadalafil and IC710 levels when dosed alone and with ketoconazole
From pages 43 and 47 of the sponsor's study report.

Mean effects on QTcF are shown in Table 1.

Table 1. Mean QTcF effects

QTcF	Tadalafil 20 mg plus	
	Ritonavir 600 mg bid N=3	**Ketoconazole 400 mg qd N=12**
Baseline	404±14	391±19
Δ @2h	-5±16	-4±19
Δ @24h	9±19	3±11

This study was useful in documenting the pharmacokinetic implications of 3A4 inhibition, but it was woefully underpowered to detect a small effect on repolarization.

Study LVFB, entitled "An Investigator- and Subject-Blind, Placebo-Controlled Study to Assess the Electrophysiologic Effect of 100 mg IC351 or Placebo on QT Interval with Ibutilide as an Open-Label Positive Control in Healthy Male Subjects", is described in a study report dated 17 June 2003. The trial protocol herein summarized is based on the fully revised protocol and amendments dated 27 September 2002 to 29 April 2003. Subjects were enrolled between 3 January 2003 and 1 May 2003, so only the amendments after the start of enrollment will be described.

Approximately 90 normal adult male volunteers were to receive, in random order and blinded fashion, single doses of oral placebo, IV ibutilide 2 µg/kg over 10 minutes, and oral tadalafil 100 mg (five-fold higher than the highest proposed dose for marketing). For two days prior to oral dosing, ECGs (standard 12-lead) were collected at sampling times to match the day of study drug administration, 0, 3, 4, 6, and 24 hours, with 10 ECGs being collected at one-minute intervals at each time point[1]. ECGs were centrally read. QT intervals were determined automatically (Marquette MUSE) and then 100% over-read. The sponsor's calculations predicted a 98% chance of demonstrating the 90% confidence limits on the tadalafil-placebo difference would exclude 10 ms (if the true effect were zero). There were no interim analyses.

Amendment 5, implemented days after the start of enrollment, added ECGs at 9 and 12 hours after dosing. Amendment 6 (29 April 2003) presented the final analysis plan, including analyses based on Fredericia, Lillie (exponent of 0.413), and individualized correction of QT, and categories of outliers.

Seventeen subjects participated in a study intended to help select the dose of ibutilide.

The study was conducted at two sites in the UK and one in the US. All 99 subjects were males age 18 to 53. These included replacements for 4 of the 9 subjects who withdrew. Details of the withdrawals are given on page 36 of the sponsor's study report; none appear to be related to proarrhythmia associated with tadalafil.

Plasma levels of tadalafil and major metabolites show adequate sampling times for ECGs relative to parent drug, but the major metabolite's concentration is highest at the final (24 hours) assessment.

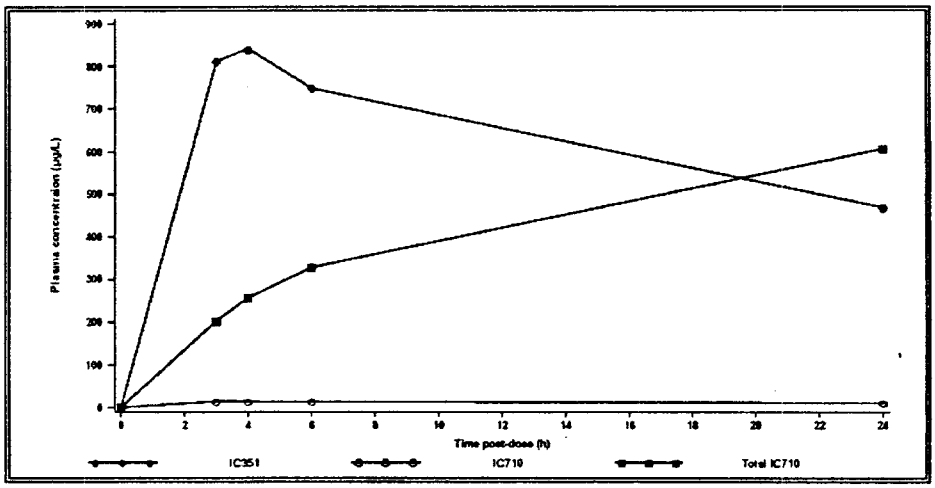


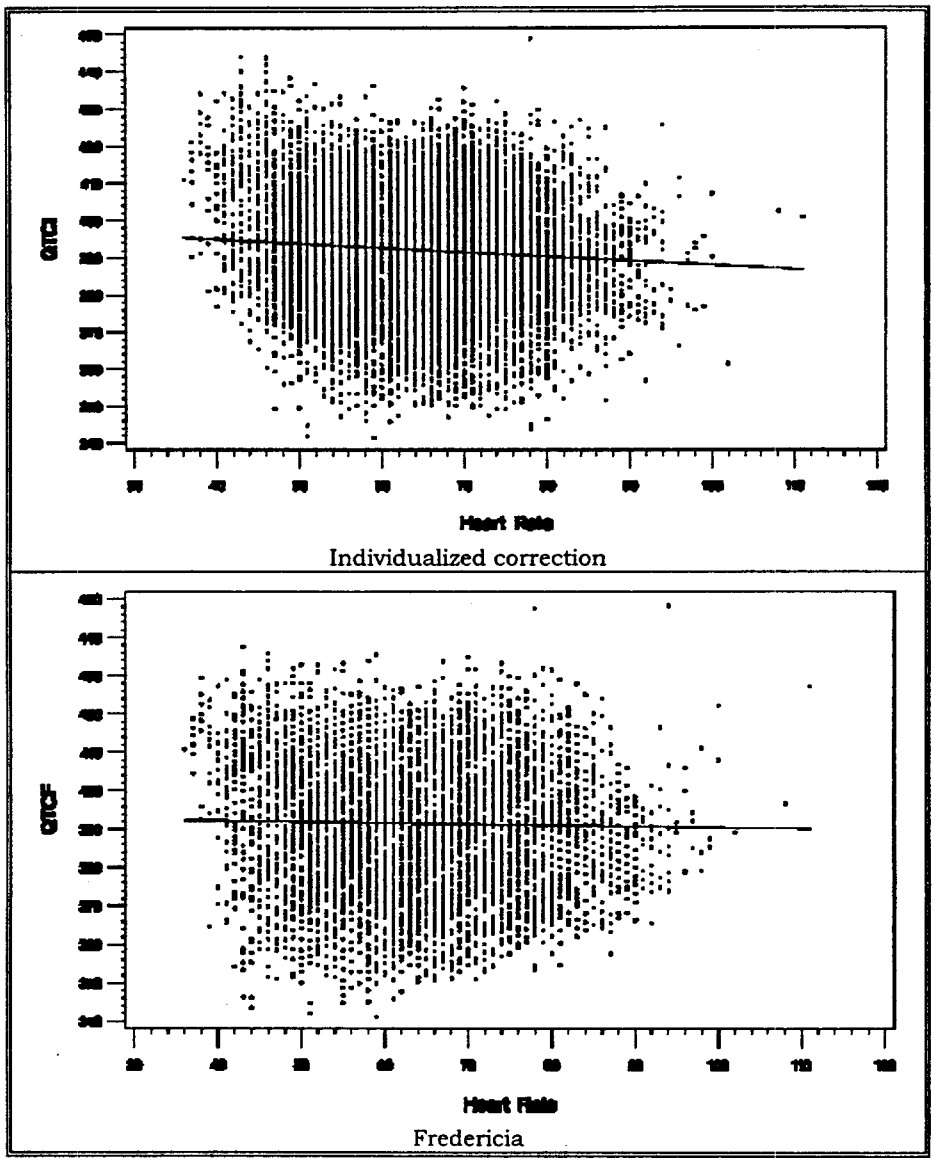
Figure 3. Geometric mean plasma concentrations of tadalafil and metabolites

Figure from page 152 of sponsor's study report.

The sponsor's figures for individual data do not reveal marked outliers for plasma drug levels.

Plots of the relationship between QTc and heart rate at baseline for various correction methods are shown in Figure 4.

[1] *Baseline ECGs ended prior to drug administration. For all other times, the 10 ECG replicates were centered on the nominal time point.*



Individualized correction

Fredericia

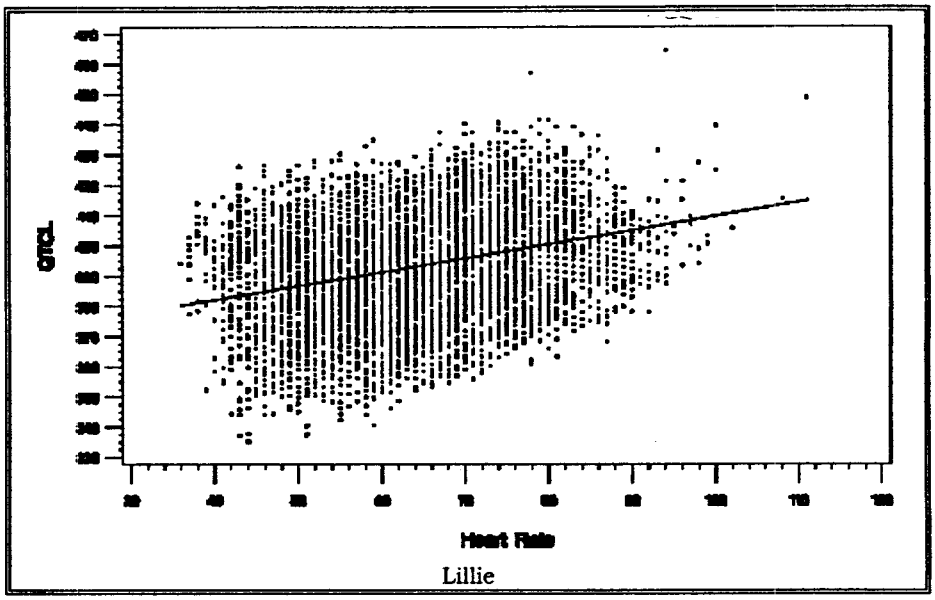


Figure 4. Baseline relationship between QTc and heart rate

Figures reproduced from sposnor's study report pages 268-270.

The relationship is most nearly flat for Fredericia.

Various estimates of the effect on QTc at various times after dosing are shown in Table 2.

Table 2. Change from baseline and placebo in QTc[2]

Time	ANOVA		Individualized		Fredericia	
(h)	Mean	90% CI[3]	Mean	90% CI	Mean	90% CI
3	4.3	2.6-5.9	3.3	1.7-4.9	3.9	2.3-5.5
4	3.6	1.9-5.2	3.1	1.5-4.7	3.5	1.9-5.1
6	4.0	2.4-5.6	3.5	1.9-5.2	4.6	3.0-6.2
24	2.3	0.6-3.9	1.1	-0.6-2.7	2.2	0.6-3.8

Without considering the assay validation control, it is clear that the study was amply powered to detect a small effect on QTc, as the effects of tadalafil were statistically different from zero at all time points, despite being quite small. Various analysis methods gave similar results.

The sponsor's analyses of outliers for mean effects at each nominal time point found, with various correction methods, a couple of subjects with a change from baseline in QTc of thirty-something milliseconds. No values were greater than 450 on tadalafil or placebo, but several were this high after ibutilide.

When assessed by individual ECG, relatively many ECGs had QTc values increased by >30 ms from baseline (e.g., 15% on tadalafil vs. 8% on placebo, by QTcF), but there is no reason to suspect such findings to be clinically relevant or even treatment-related.

Plots of change in QTcI versus plasma levels of parent or principal metabolite give no hint of a relationship.

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[2] Data from pages 157-159 of the sponsor's study report.

[3] The 95% confidence limits are somewhat wider than the 90% limits computed by the sponsor. If the data were normally distributed, the difference would be about a factor of 1.19.

Study LVFB was conducted with a dose of tadalafil producing plasma levels higher than usually achieved with the highest recommended dose, 20 mg, coupled with 3A4 inhibition. Study LVFB was able to detect incontrovertible evidence of a small effect, on repolarization, 3 to 6 ms, with no outliers. What mortal risk does this level of QT prolongation represent? While it is not possible to exclude risk associated with small effects on repolarization, there are no known examples of manifest risk associated with drugs that produce an effect of this magnitude. Any risk there may be is apt to be no greater than for other risks implicit in a clinical experience of the present size.

The Division of Reproductive and Urologic Drug Products is welcome to contact the Division of Cardio-Renal Drug Products for further clarification or discussion.

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/s/

Norman Stockbridge
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MEDICAL OFFICER

Doug Throckmorton
7/8/03 09:44:42 AM
MEDICAL OFFICER

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Consultative Clinical Review

NDA: 21-368 (Cialis; tadalafil)

Sponsor: Lilly ICOS

Submission: Definitive QT protocol LVFB

Review date: 4 February 2003

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

Distribution: NDA 21-368
HFD-580/Spell-LeSane
HFD-580/Hirsch

This is the seventh formal consultative review on tadalafil and the fourth review on the QT issue.

The maximum dose of tadalafil for which approval is being considered is 20 mg, not more than once per day. Plasma levels of the parent drug peak 2-4 hours or so after dosing. Peak plasma levels of the principal metabolite, methylglucuronide, are said to peak at about 24 hours. Tadalafil is said to have a half-life of about 18 hours. The pharmacokinetics of tadalafil are linear up to about 20 mg, but they are distinctly less than linear at higher doses, so that at 500 mg, the highest dose for which data are available, Cmax is only about 3-fold higher than observed at 20 mg. Tadalafil is a substrate for 3A4, but plasma levels rise modestly with 3A4 inhibition.

The sponsor was unable to allay concerns about potential QT effects on the basis of previous studies conducted without an assay-validating control.

To address concerns about whether tadalafil may be arrhythmogenic, Lilly has submitted (11 October 2002) protocol LVFB, entitled "An investigator and subject blind, placebo controlled study to assess the electrophysiologic effect of 100 mg IC351 or placebo on QT interval with ibutilide as an open-label positive control in healthy male subjects". The sponsor shared an earlier draft of this protocol with me and I supplied some informal comments to the sponsor.

The proposed study will be conducted in 90 healthy male volunteers who will receive, in random order, single oral doses of placebo and tadalafil 100 mg (5 times the maximum recommended dose), and intravenous ibutilide (at a dose to be determined by a pilot study). Prior to each study drug administration, subjects will have baseline ECGs collected for 3 days at times corresponding to times on study days—0, 3, 4, 6, and 24 hours (and 8, 10, and 12 minutes after ibutilide infusion).

ECG recordings will be interpreted by a central ECG vendor who will be blinded to treatment. A detailed methodology for QT assessment is not provided. The primary analysis will use RR interval as a covariate. Secondary analyses will be based on QT correction for heart rate using Fridericia and Lillie ($RR^{-0.413}$) factors.

The use of a dose 5-fold higher than planned for marketing is pretty reassuring, particularly since plasma levels rise less than linearly with higher doses.

The plan is predicated on ruling out an effect on QT as large as 10 ms. This is also adequately reassuring, considering the clean preclinical data, the lack of proarrhythmic events in the clinical development program, and other information available to DRUDP on QT effects of other PDE V inhibitors.

Because of time constraints, this review has not received concurrence from the Director of the Division of Cardio-Renal Drug Products.

The Division of Reproductive and Urologic Drug Products is welcome to contact the Division of Cardio-Renal Drug Products for further clarification or discussion.

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Norman Stockbridge
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MEDICAL OFFICER

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Consultative Clinical Review

NDA: 21-368 (Cialis; tadalafil)

Sponsor: Lilly ICOS

Submission: Reanalysis of QT data.

Review date: September 19, 2002

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

Concurrence: Douglas Throckmorton, M.D., Division Director

Distribution: NDA 21-368

HFD-580/Spell-LeSane

HFD-580/Hirsch

This is the sixth formal consultative review on tadalafil and the third review on the QT issue.

To address concerns about whether tadalafil may be arrhythmogenic, Lilly has submitted (12 September 2002) the results of retrospective analyses of three studies.

The maximum dose of tadalafil for which approval is being considered is 20 mg, not more than once per day. Plasma levels of the parent drug peak 2-4 hours or so after dosing. Peak plasma levels of the principal metabolite, methylglucuronide, are said to peak at about 24 hours. Tadalafil is said to have a half-life of about 18 hours. The pharmacokinetics of tadalafil are linear up to about 20 mg, but they are distinctly less than linear at higher doses, so that at 500 mg, the highest dose for which data are available, Cmax is only about 3-fold higher than observed at 20 mg. Tadalafil is a substrate for 3A4, but plasma levels rise modestly with 3A4 inhibition.

The three studies subjected to reanalysis were as follows:

Study LVBG was a double-blind study in which subjects with erectile dysfunction were randomized to placebo or tadalafil 10, 25, 50, or 100 mg once daily for 21 days. There are about 50 subjects in the 50- and 100-mg arms with 12-lead ECGs at baseline and at 24 hours after the last dose.

Study LVBS was a fairly conventional first-in-man study. In double-blind fashion, cohorts of 4 normal male volunteers received, in random order, single ascending doses of placebo or 3 dose levels of tadalafil. Overall, 4 subjects received placebo plus 50, 250, and 500 mg and 8 subjects received 100 mg. ECGs were obtained at baseline and 0.5, 1, 2, 4, 8, 12, and 24 hours after dosing.

Study LVBU was a double-blind, parallel-group study in which normal volunteers received placebo (n=13), single doses of tadalafil 50 mg (n=14), or 50 mg for 7 days

(n=8). ECGs were obtained at baseline and at 1, 6, 12, and 24 hours after the first and last doses.

The sponsor has performed a variety of analyses by, dose, time, and plasma level of tadalafil. For example, the relationship between plasma level and QTcF for study LVBS is shown in Figure 1.

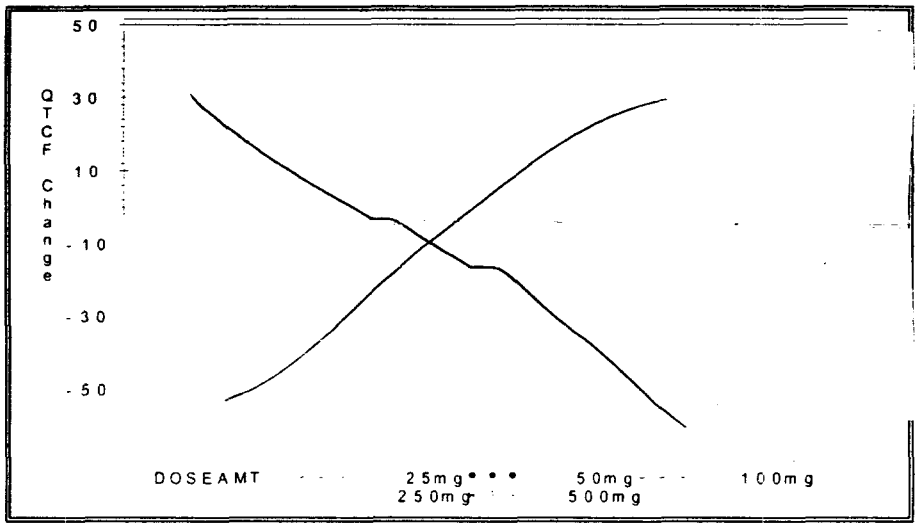

Figure 1. QTcF by plasma level of tadalafil (Study LVBS)

Sponsor's analysis. Figure from submission page 34.

These data reveal no trend for an increasing QT with plasma level. Furthermore, the data reveal no trend for outliers in the positive direction with plasma level.

Despite the fact that most of the QT assessments were made more than 24 hours after dosing in study LVBG, repetitive dosing and a long half-life produced a useful range of plasma levels in this study, too. The relationship between QTcF and plasma level of tadalafil for this study is shown in Figure 2.

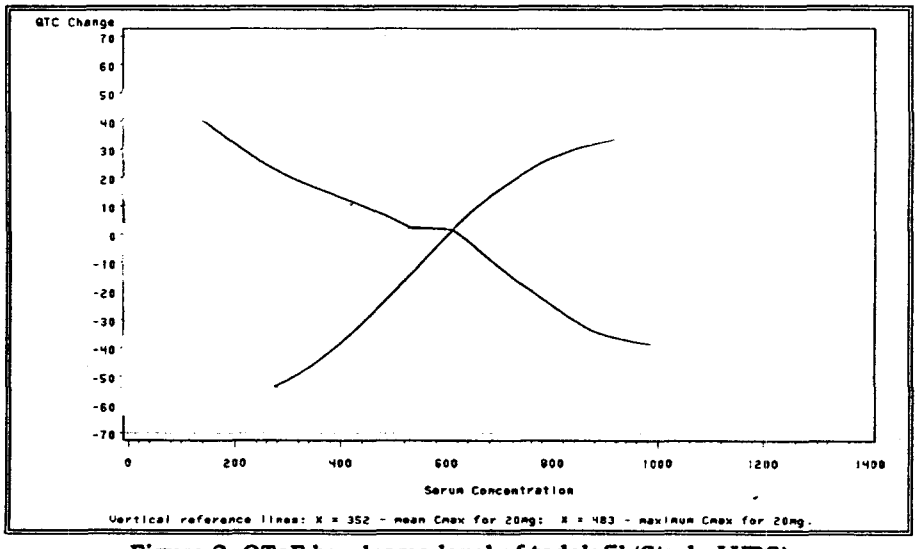

Figure 2. QTcF by plasma level of tadalafil (Study LVBG)

Sponsor's analysis. Figure from submission page 65.

Fewer data are available for study LVBU, but they look quite similar to the other two studies.

The Division of Cardio-Renal Drug Products concurs with the sponsor's conclusion that these data are consistent with ECG data previously reviewed and that there are no indications of an effect on QT by tadalafil.

Furthermore, one can take some comfort from the considerably less-than-linear increase in plasma levels with dose and the modest effects of 3A4 inhibition (assuming these interpretations of the pharmacokinetic data are confirmed by the biopharmaceutists), because they suggest that, despite a lack of dose-limiting adverse events, it is difficult to generate high plasma levels of drug in plasma.

There are two weaknesses of these data. First, they are based on few subjects, so one is concerned about missing outliers. And, second, it is not possible to specify what magnitude of mean effect on QT these data exclude.

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Norman Stockbridge
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Doug Throckmorton
9/20/02 03:53:19 PM
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DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Consultative Clinical Review

NDA: 21-368 (tadalafil)

Sponsor: Lilly ICOS

Submission: Proposed clinical study evaluating nitrate interaction; revised protocol submitted 22 August 2002.

Review date: September 6, 2002

Reviewer: N. Stockbridge, M.D., Ph.D

Concur: Douglas Throckmorton, M.D., Division Director, HFD-110

Distribution: NDA 21-368

HFD-580/Division Director

HFD-580/Sherrod/Hirsch/Olmstead/Batra

Protocol LVDN was submitted to address the deficiency in the NDA related to adequate characterization of the interaction of tadalafil and organic nitrates. The sponsor's proposed study is a two-period crossover in which 150 normal male volunteers over age 40 would receive, in random order, placebo or tadalafil 20 mg (maximum recommended dose) for 7 days, and then challenge doses of sublingual nitroglycerin at 4, 8, 12, 24, 48, and 72 hours after the last dose of tadalafil. The primary end point is a categorical assessment of blood pressure (<85 mmHg standing systolic) evaluated at each time point.

Other than the proposed exclusion of diabetics, this protocol appears to satisfy DRUDP's requirements. DCRDP believes this trial will yield useful data informing the safe use of nitroglycerin after tadalafil.

If the Division of Cardio-Renal Drug Products can be of further assistance, please contact us again.

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Norman Stockbridge
9/6/02 02:55:10 PM
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Doug Throckmorton
9/12/02 08:14:50 AM
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DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Consultative Clinical Review

NDA: 21-368 (tadalafil)

Sponsor: Lilly ICOS

Submission: Study of exercise tolerance in men with stable coronary artery disease.

Review date: August 8, 2002

Reviewer: N. Stockbridge, M.D., Ph.D

Concur: Douglas Throckmorton, M.D., Division Director, HFD-110

Distribution: NDA 21-368

HFD-580/Division Director

HFD-580/Spell-LeSane/Hirsch/Olmstead/Batra/Benson

Background

Tadalafil is a PDE5 inhibitor, similar to sildenafil, with an "approvable" action on its NDA for the treatment of erectile dysfunction. This is the fourth consult request on this NDA. Prior consults have dealt with evaluation of QT data (reviewed 12 March 2002), a proposed nitrate interaction study (reviewed 17 May 2002), and a proposed QT reanalysis plan (reviewed 16 July 2002). DCRDP is now asked to review an exercise tolerance study.

Response

Study LVCP, entitled "Evaluation of IC351 during exercise stress testing in patients with coronary artery disease" is described in a full final study report, dated 9 November 2001, submitted to NDA 21-368 on 28 June 2002. A part of the full report is the fully amended study protocol (5 June 2000, amended to 2 January 2001[1]), and the report is accompanied by an apparently complete set of electronic datasets.

The study was conducted between October 2000 and February 2001 at one center in Scotland and one in Netherlands.

Subjects were to be males or females with demonstrated ischemia on a previous treadmill stress test while receiving regular medical therapy excluding nitrates, history of angina within 3 months, and history of use of nitrates for angina within 9 months. Subjects were excluded for history of erectile dysfunction needing treatment within 6 months, prior exposure to tadalafil within 30 days, use of sildenafil within 7 days, history of hypotension during an ETT, blood pressure outside 90/60 to 170/115 mmHg, MI within 30 days, PCI within 14 days, CABG within 60 days, uncontrolled arrhythmia, need for nitrates within 24 hours of study, need for digoxin, cardiac pacemaker, conduction defects, unstable angina within 30 days, or heart failure within 30 days.

Subjects were screened for hypotension following a dose of sublingual nitroglycerin 0.4 mg, after which subjects underwent a treadmill ETT (modified Bruce protocol),

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[1] This document serves as the basis of the description of the protocol. The two amendments were minor clarifications of intent.

wherein subjects were expected to exercise until 1.5 mm ST depression or limiting chest pain. Qualifying subjects were to have two on-treatment stress tests, receiving, in random order, placebo or tadalafil 10 mg 2 hours prior to ETT. The 2 crossover periods were to be separated by 4 to 10 days. Unless there was hypotension manifested during the ETT (an exclusion if it happened at screening), subjects would receive sub-lingual nitroglycerin 0.4 mg immediately after the ETT, with vital signs followed for 1 hour or until they returned to within 10% of the pre-test baseline.

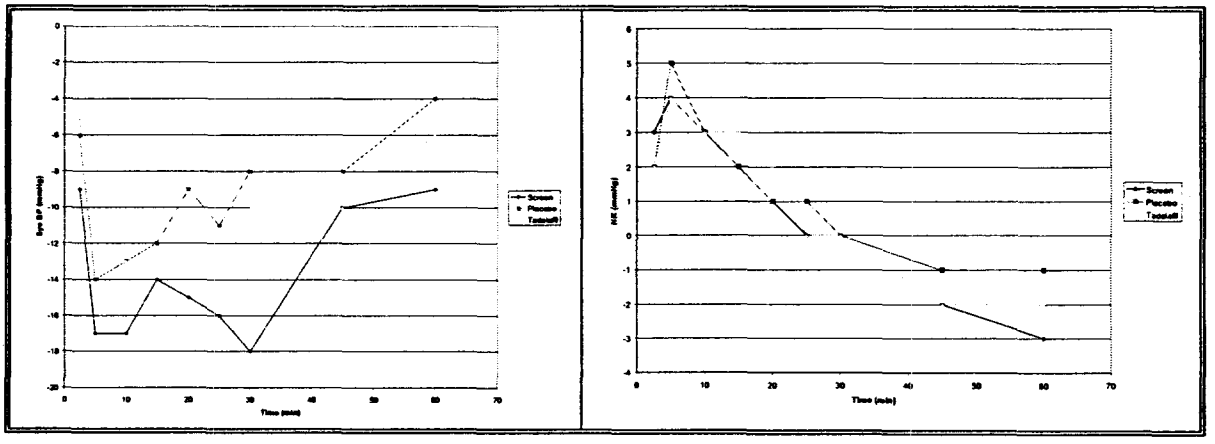
Study drug was to be considered not-inferior to placebo if the (tadalafil minus placebo) difference in time to onset of ischemia excluded -1 minute (95% one-sided confidence interval). A similar analysis of total exercise time was considered "exploratory".

Change in maximal decrease in sitting systolic pressure following nitroglycerin administration was also analyzed by a non-inferiority test with an 8-mmHg margin and 95% one-sided confidence interval.

The statistical plan describes no justification for the non-inferiority margin and no power calculation justifying planned enrollment[2].

Twenty-three subjects (22 in Scotland) enrolled and completed the study. They were 18 males and 5 females, age 53 to 74 years, 96% Caucasians. Subjects were receiving a variety of drugs typical for their condition—beta-blockers, calcium channel blockers, cholesterol-lowering agents, and nitrates. No protocol violations are described (although 5 subjects remained in the study despite exceeding the protocol-specified maximum blood pressure reduction during the screening exposure to nitroglycerin).

The mean (±SD) exercise times to ischemia[3] were 811±128 s on placebo and 816±119 s on tadalafil, remarkably similar[4], and ruling out, by the sponsor's analysis, a difference as large as 15 s.



• **Figure 1. Changes from baseline in systolic pressure and heart rate in response to NTG[5]**

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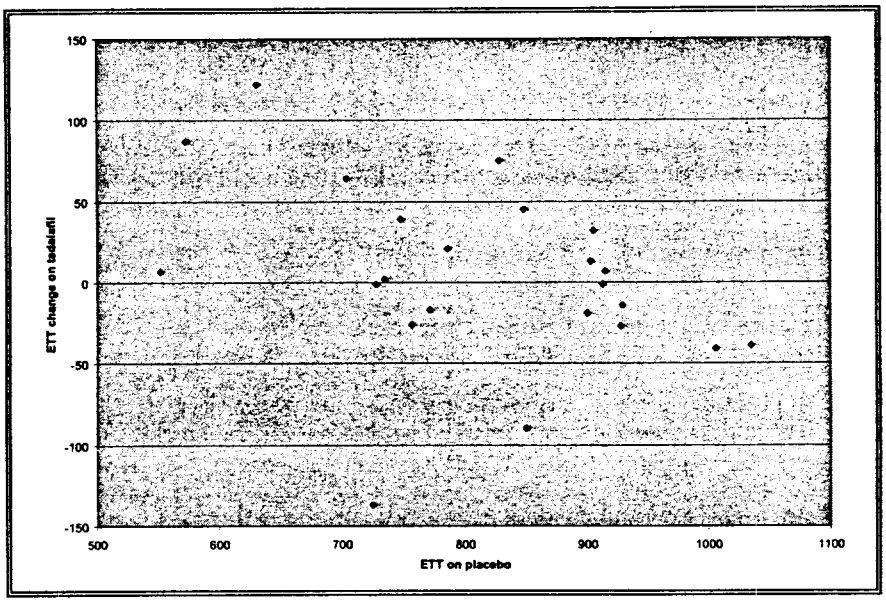
[2] Based upon an estimated 2.25-minute standard deviation, the sponsor, in the study report, estimated that, with 22 subjects completing, the study had 90% power to detect a 1-minute treatment difference.

[3] All subjects had ≥1.5 mm ST depression during the screening ETT. Three subjects did not manifest ischemia during the ETT of the tadalafil period and one did not manifest ischemia during the placebo period. It appears that the sponsor used the total exercise time for these subjects.

[4] It typically takes a trial twice this size to even detect the effect of a nitrate in such a study. This result is plausible, however, a testament to doing single-center studies.

Outliers for an effect of tadalafil on ETT were investigated by plotting the change in exercise time (tadalafil minus placebo) as a function of exercise time on placebo, shown in Figure 2.



• **Figure 2. Change in exercise time by exercise time on placebo[6].**

The figure shows some regression to the mean (tendency for small values on placebo to show higher values on tadalafil and vice versa), but no real outliers.

These data do not suggest a significant interaction between tadalafil and nitroglycerin when the tadalafil is administered (as in this case) at 10 mg about 3 hours prior to challenge with nitroglycerin. This is a mystery (receptor specificity?) given tadalafil's 17.5-hour mean plasma half-life.

The biphasic heart rate response is also a mystery. On study days, it might be the result of superimposing the nitroglycerin response on the recovery from exercise, but the same phenomenon appears on the screening visit, wherein the response to nitroglycerin was assessed prior to exercise testing.

There were no deaths or discontinuations for adverse events or other reasons.

Nine subjects reported 15 mild-moderate adverse events following tadalafil and 5 subjects reported 6 mild-moderate adverse events after placebo. The only event reported by more than one subject was headache (3, all on tadalafil).

Although this is a small study providing limited confidence, it raises no concerns about the effect of tadalafil 10 mg alone on exercise ability is patients with coronary artery disease, nor does it raise concerns about the use of nitrates 3 hours after a 10-mg dose of tadalafil.

The Division of Cardio-Renal Drug Products appreciates the opportunity to consult on this drug. DRUDP is welcome to contact DCRDP for further clarification or follow-up.

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[5] Reviewer's plot of sponsor's analysis.

[6] Reviewer's analysis.

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Norman Stockbridge
8/9/02 08:38:14 AM
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Doug Throckmorton
8/12/02 03:22:24 PM
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DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Consultative Clinical Review

NDA: 21-368 (Cialis; tadalafil)

Sponsor: Lilly ICOS

Submission: Proposal for reanalysis of QT data.

Review date: July 16, 2002

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

Concurrence: Douglas Throckmorton, M.D., Division Director

Distribution: NDA 21-368

HFD-580/Spell-LeSane

HFD-580/Hirsch

In a partial response to the action letter for tadalafil, the sponsor has proposed retrospective analysis of some of the QT interval data obtained in normal volunteers and subjects with erectile dysfunction. The Division of Cardio-Renal Drug Products is asked to comment on this analysis plan.

The maximum dose of tadalafil for which approval is being considered is 20 mg, not more than once per day. Plasma levels of the parent drug peak 4 hours or so after dosing. Peak plasma levels of the principal metabolite, methylglucuronide, peak at about 24 hours.

The three studies to be considered for reanalysis are as follows:

Study LVBG was a double-blind study in which subjects with erectile dysfunction were randomized to placebo or tadalafil 10, 25, 50, or 100 mg once daily for 21 days. There are about 50 subjects in the 50- and 100-mg arms with 12-lead ECGs at baseline and at 24 hours after the last dose.

Study LVBS was a fairly conventional first-in-man study. In double-blind fashion, cohorts of 4 normal male volunteers received, in random order, single ascending doses of placebo or 3 dose levels of tadalafil. Overall, 4 subjects received placebo plus 50, 250, and 500 mg and 8 subjects received 100 mg. ECGs were obtained at baseline and 0.5, 1, 2, 4, 8, 12, and 24 hours after dosing.

Study LVBU was a double-blind, parallel-group study in which normal volunteers received placebo (n=13), single doses of tadalafil 50 mg (n=14), or 50 mg for 7 days (n=8). ECGs were obtained at baseline and at 1, 6, 12, and 24 hours after the first and last doses.

There are not many subjects in this set of three studies, particularly for evaluation of effects near the time of peak plasma levels of tadalafil, so it would be remarkable if any analysis of these data could provide the sought assurance.

The sponsor expects there is no effect of tadalafil on QT interval, but the studies have no positive control to establish assay sensitivity. The sponsor proposes to compensate for this problem by deriving assay sensitivity from the baseline data. How this is to be done is not specified in detail, but the idea is to use the relationship between QT and RR at baseline for the various groups to determine what level of QT change was detectable. This idea cannot be dismissed out of hand, but the sponsor should propose the details for such a procedure.

Do the sponsor's proposals adequately address the QT problem? The data are few, but in some cases, one is looking at high multiples of the to-be-marketed high dose. The sponsor's task is to exclude an effect of some magnitude at doses greater than or equal to some reasonable multiple of 20 mg. It remains to be shown how this can be done.

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DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Consultative Clinical Review

NDA: 21-368 (tadalafil)

Sponsor: Lilly ICOS

Submission: Proposed clinical study evaluating nitrate interaction.

Review date: May 17, 2002

Reviewer: N. Stockbridge, M.D., Ph.D

Concur: Douglas Throckmorton, M.D., Division Director, HFD-110

Distribution: NDA 21-368

HFD-580/Division Director

HFD-580/Sherrod/Hirsch/Olmstead/Batra

Background

Tadalafil is a PDE5 inhibitor, similar to sildenafil, with an "approvable" action on its NDA for the treatment of erectile dysfunction. There is a well-understood pharmacological mechanism by which PDE5 inhibition potentiates the action of organic nitrates. The sponsor has been requested to formally evaluate the interaction with organic nitrates, specifically to address the question of when, after a dose of tadalafil, it is safe to administer organic nitrates.

Response

In a previous teleconference with the sponsor, it was argued that the appropriate goal of such a study was to define the blood pressure response to a test dose of nitrate as a function of the time interval between the doses of tadalafil and nitrate. Together with a dose-response curve for nitrate alone, one could work out a dose of nitrate appropriate to produce a given effect on blood pressure for any given time from a dose of tadalafil.

The sponsor's proposed study (protocol H6D-EW-LVDN(a) does something entirely different. In a crossover design, 150 subjects will receive 7 daily doses of the to-be-marketed dose of tadalafil followed by test doses of sublingual nitroglycerin at 6, 24, 48, 72, and 96 hours. The proposed primary end point is the fraction of subjects experiencing a specified degree of hypotension.

These are very different objectives. The sponsor seeks to reassure one that a conventional dose of nitroglycerin will not produce inordinate hypotension if it is delivered long enough after a dose of tadalafil. This reviewer's proposal had been to characterize the hemodynamic response as a function of intervening time. Of course, some of the data pertinent to this reviewer's objective can be obtained from the sponsor's proposed study, but the only pertinent times are, probably, 6 and (perhaps) 24 hours, whereas this reviewer had sought to characterize somewhat more fully the time course over the first 24 hours.

[redacted]

The Division of Cardio-Renal Drug Products appreciates the opportunity to consult on this drug. DRUDP is welcome to contact DCRDP for further clarification or follow-up.

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DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Consultative Clinical Review

NDA: 21-368 (Cialis; tadalafil)

Sponsor: Lilly ICOS

Submission: NDA amendment; updated summary of QT data.

Review date: March 12, 2002

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

Concurrence: Douglas Throckmorton, M.D., Division Director

Distribution: NDA 21-368

HFD-580/Spell-LeSane

HFD-580/Hirsch

The Division is asked to comment on the evidence of arrhythmogenic potential in the NDA for tadalafil, a new molecular entity and analog of sildenafil, developed for the treatment of erectile dysfunction.

According to the sponsor's summary, tadalafil and sildenafil block HERG IKr channels at concentrations many times higher than typical plasma concentrations.

Tadalafil was administered to beagle dogs at up to 400 mg/kg/day for 26 weeks without evidence of a systematic effect on QT.

The absolute bioavailability of tadalafil is not known, but apparently there is no food effect. Complete inhibition of CYP P450-3A4 (with ketoconazole) results in approximately doubling the plasma levels of tadalafil. Moderate hepatic impairment doubles the mean peak plasma levels. Mild-to-moderate renal impairment has a smaller effect. Other factors that might affect plasma levels (e.g., other enzyme inhibition) are not described.

ECG data (SAS datasets) were provided for (logically) 8 studies conducted under 7 protocols. These studies all involved normal volunteers who received up to 10 days of sequential dosing at 2.5 to 40 mg once daily.

Table 1. Studies considered.

Study	Design	N	Doses
LVAN	3-period crossover, single doses	18	Placebo, 10, 20
LVAU	Parallel, 1 & 10 days	37	Placebo, 5, 10
LVBXA	4-period crossover, single doses	16	10
LVBXB	4-period crossover, single doses	16[1]	2.5, 5, 10, 20
LVCS	4-period crossover, single doses	72	Placebo, 5, 10, 20, 40
LVDK	One group, 1 & 10 days	80	Placebo, 10, 20
LVDL	2-period, single doses	20	20
LVDQ	2-period, single doses	18	20

Each study had, at least, ECGs recorded at baseline and several hours after doing. The latter recording is assumed to be around the time of the peak plasma levels.

(Two other PK interaction studies are not considered [redacted] Five phase III studies also had ECG data collected, but not in a known close temporal relationship to dosing.)

There is no clinically significant treatment effect on heart rate, as shown in Table 2.

Table 2. Treatment effects (mean±SD) on heart rate[2].

0 mg N=1954	2.5 mg N=248	5 mg N=317	10 mg N=460	20 mg N=453	40 mg N=45
60.2±9.0	58.6±8.5	58.7±8.7	59.3±8.9	59.6±9.0	58.4±5.8

The relationship between QT and heart rate is shown in Figure 1. The zero-dose measurements included all subjects' screening data, all baseline assessments, and the on-treatment values with a zero dose.

[1] *Same subjects in Studies LVBXA and LVBXB.*

[2] *Reviewer's analysis. N gives number of measurements, not number of subjects.*

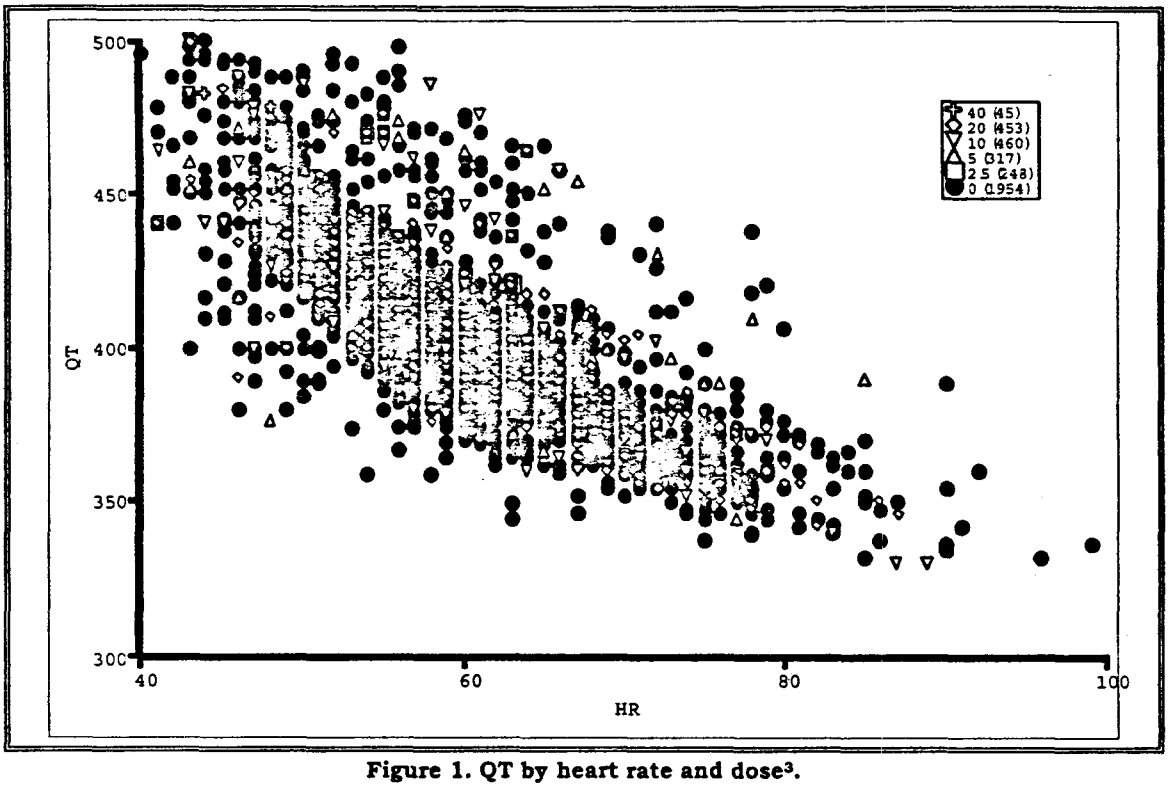

Figure 1. QT by heart rate and dose[3].

There does not appear to be any systematic effect of dose on the relationship between QT and heart rate.

In two studies, there were subjects with on-treatment ECGs following administration of both placebo and a non-zero dose. These data permit an analysis of the distribution in changes in QTc from baseline and placebo (double-difference), as shown in Figure 2.

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[3] *Reviewer's analysis.*

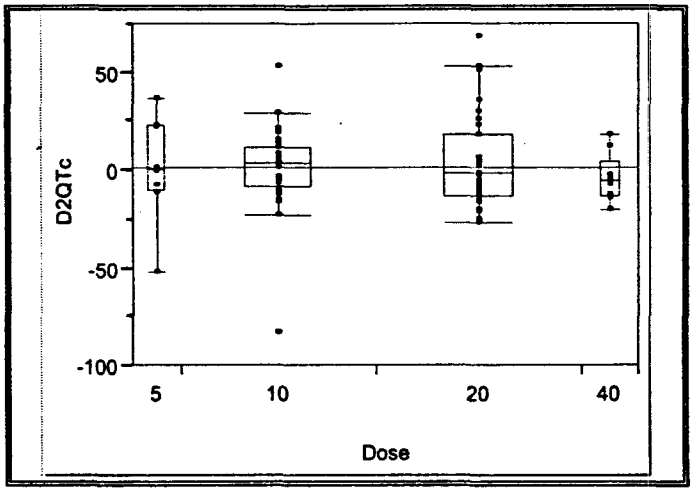

Figure 2. Change from baseline and placebo for QTc.

Reviewer's analysis. Only subjects with on-treatment data on a zero and non-zero dose contributed to this analaysis. On-treatment values of sponsor-calculated QTc were subtracted from values at baseline. Then the difference was calculated for the subject's non-zero dose minus the value on zero dose.

Although there appears to be no relationship between dose and QTc, the large standard deviation makes it impossible to rule out a clinically significant treatment effect.

There is one other PK study of potential interest, but for which electronic data are not provided. Study LVBS was a 4-period crossover study with 4 ascending dose cohorts in which normal volunteers received placebo and doses of tadalafil between 1 and 500 mg. ECG monitoring was continuous for the first 4 hours after dosing and there were 12-lead ECGs performed at 0.5, 1, 2, 4, and 8 hours after dosing, and later times. Despite its small enrollment (17 subjects total, 4 on the 500-mg dose), the highest dose was higher and the intensity of monitoring was greater than in the subsequent studies. It might be useful to review this study in greater detail.

The clearest study to interpret would be one in which there was an active control arm, successfully detected. These trials have no such arm.

The observed variation in QT or QTc makes it impossible to rule out a clinically significant, even substantial, treatment effect, although the nominal result shows no effect.

The highest dose evaluated is only twice the apparent expected dose to be used clinically. This is not a comforting safety margin. Consideration should be given to expected usage patterns (what will limit dose?), metabolic factors that might produce substantially greater than mean plasma levels of drug (CYP 3A4 inhibition), whether there may be *electrophysiologically* active metabolites (e.g., methylcatechol glucuronide), and thus whether ECGs taken 2-3 hours after dosing had the optimum potential to see electrophysiological effects.

The sponsor's Integrated Summary of Safety cites 7 subjects in PK/PD studies as having a total of 11 syncopal episodes, all on active treatment. Four subjects (6 incidents) were receiving tadalafil or sildenafil in association with nitrates. The other cases were thought to be vasovagal, but it would be worthwhile to review these cases and any available ECG data. In phase III studies, there were 3 cases of syncope on placebo (0.25%) and a case on tadalafil (<0.1%).