CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-368

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review
Division of Pharmaceutical Evaluation II

NDA:	21-368
Product Trade Name:	Cialis™
Active Ingredient:	Tadalafil (5, 10 and 20 mg IR tablets)
Indication:	Male erectile dysfunction
Sponsor:	Lilly ICOS LLC
Date(s) of Submission:	May 27, 2003, June 5, 2003, June 24, 2003, July 22, 2003, August 11, 2003, August 29, 2003, September 11, 2003, October 9, 2003, October 15, 2003, October 20, 2003, October 24, 2003, November 5, 2003, and November 17, 2003
Type of Submission:	Response to an approvable letter
Reviewer:	Leslie Kenna, Ph.D., Venkateswa Jarugula, Ph.D.
Team Leader:	Ameeta Parekh, Ph.D.

I. Executive Summary

This submission is an amendment to NDA 21-368 for Lilly ICOS LLC's new chemical entity tadalafil (Cialis™). NDA 21-368 was submitted on June 28, 2001 and received an approvable letter dated April 29, 2002. Requests made of the sponsor in the approvable letter included the need for the sponsor to provide information regarding the interaction of 20 mg tadalafil with: (1) nitrates, (2) alcohol, (3) ketoconazole (400 mg), (4) ritonavir, (5) doxazosin or terazosin (at doses used to treat benign prostatic hypertrophy), (6) other anti-hypertensives, (7) warfarin, and (8) aspirin. Additionally, the sponsor was asked to investigate the effect tadalafil on QT interval and its potential link with myalgia and back pain. The sponsor claims that this resubmission, with components dated May 27, 2003, June 5, 2003, June 24, 2003, July 22, 2003, August 11, 2003, August 29, 2003, September 11, 2003, October 9, 2003, October 15, 2003, October 20, 2003, October 24, 2003, November 5, 2003 and November 17, 2003 is a complete response to the issues raised in the approvable letter.

It was agreed between the medical officers and the clinical pharmacology reviewers that the Clinical Pharmacology review of this NDA would address the following studies:

- LVDT: A Study to Investigate the Tolerability and Pharmacokinetics of IC351 in Subjects on Hemodialysis for Renal Failure

- LVEV: A Study to Assess the Effect of Ritonavir and Ketoconazole on the Pharmacokinetics of 20 mg IC351 (Tadalafil) in Healthy Subjects

- LVFB: 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

- LVFG: A Pharmacodynamic Study to Evaluate the Interaction Between 20 mg IC351 (Tadalafil) and 8 mg q.d. Doxazosin, an Alpha 1 Adrenergic Antagonist, in Healthy Male Subjects

• ADME Report 89 Final Report Amendment 01: In Vitro Interaction of IC351 (Tadalafil) with Human Cytochrome P450 2C19

Note that ADME Report 89 was submitted in the original filing of this NDA. It was resubmitted to note clerical changes to the document. None of the changes affected the scientific results of the study.

The reviewer of the initial submission of NDA 21-368 recommended a starting dose of 5 mg in patients with moderate renal impairment. In the resubmission dated May 27, 2003, the sponsor proposed 10 mg and 20 mg strengths of tadalafil. The need for a 5 mg dose was re-evaluated during this review cycle. A recommendation for a 5 mg dose was communicated to the sponsor during this review cycle and the sponsor provided the necessary data to launch 5 mg, 10 mg and 20 mg strengths.

RECOMMENDATION
The resubmission of NDA 21368 for tadalafil tablets is acceptable from the Clinical Pharmacology and Biopharmaceutics perspective.

Phase IV Commitments
None requested.

II. Table of Contents

III. Summary of Clinical Pharmacology and Biopharmaceutics Findings

The following table summarizes the exposure changes observed in patients with renal impairment, End Stage Renal Failure undergoing hemodialysis, and in subjects receiving potent CYP 3A inhibitors concomitantly with 20 mg tadalafil. Note that information on the metabolites of tadalafil (Total IC710) is included, as well.

	Mild Renal Impair	Moderate Renal Impair	ESRF with Dialysis	+ Ritonavir 200 mg BID	+ Ketoconazole 400 mg QD
AUC change (Tadalafil)					
5 mg	2.1-fold ↑	2.1-fold ↑	No change (14% ↓ or 1.1-fold ↑)		
10 mg	2.2-fold ↑	1.7	1.1-4.8-fold ↑		
20 mg			2.7 -fold ↑	2.6-fold ↑	4.1-fold ↑
Cmax change (Tadalafil)					
5 mg	1.1-fold ↑	1.3-fold ↑	22% ↓		
10 mg	1.2-fold ↑	1.2-fold ↑	0-2.2-fold ↑		
20 mg			1.9-fold ↑	No change	1.2-fold ↑
AUC change (Total IC710)					
5 mg	2.2-fold ↑	3.6-fold ↑	2.7-fold ↑		
10 mg	2.6-fold ↑	3.6-fold ↑	2.1-3.3-fold ↑		
20 mg				64% ↓	25% ↓
Cmax change (Total IC710)					
5 mg	1.3-fold ↑	1.6-fold ↑	1.6-fold ↑		
10 mg	1.3-fold ↑	1.6-fold ↑	1.3-1.8-fold ↑		
20 mg				80% ↓	62% ↓

Summary of Exposure Changes Observed in Patients with Renal Impairment, End Stage Renal Failure Undergoing Hemodialysis, and in Subjects Receiving Potent CYP 3A Inhibitors Concomitantly with Tadalafil. Total IC710 accounts for the active metabolites of tadalafil.

Based on exposure information and adverse event reports submitted, a 5 mg daily dose is recommended in subjects with End Stage Renal Failure (ESRF) receiving dialysis or in subjects with moderate renal impairment. Based on parent exposure data alone, a 10 mg dose may be dosed once every 48 hours in subjects with mild or moderate renal impairment, but studies suggest that it may be poorly tolerated with respect to back pain. Dialysis contributed negligibly to the elimination of tadalafil.

Of the CYP 3A substrates studied, coadministration of 20 mg tadalafil with 400 mg QD ketoconazole caused the most significant CYP 3A drug-drug interaction with respect to increase in tadalafil exposure. Once daily administration of 400 mg ketoconazole caused $AUC_{0\rightarrow\infty}$ to increase 4.1-fold and Cmax to increase 1.2-fold. Administration of 200 mg BID ritonavir resulted in a mean 2.6-fold increase in AUC and no change in mean Cmax. The recommendation based on these results is that subjects taking potent CYP 3A

inhibitors—such as ketoconazole and ritonavir—should not exceed a dose of 10 mg tadalafil once in every 72 hours.

Tadalafil has a clinically significant effect on blood pressure when coadministered with the alpha-1 adrenergic antagonist, doxazosin. As such, the use of tadalafil should be contraindicated in patients receiving doxazosin. There was no evidence of a clinically significant pharmacodynamic interaction between tadalafil and an alpha-1A adrenergic antagonist (tamsulosin) in a study with eighteen (18) healthy male subjects, based on maximum supine systolic and diastolic blood pressure. The findings for other pharmacodynamic parameters (including mean, minimum and maximum values of standing systolic and diastolic blood pressure and supine and standing heart rate) supported this conclusion. Based on a potential class effect and given the size of the tamsulosin trial, tadalafil should be used with caution in subjects receiving tamsulosin.

In this resubmission, the sponsor provided the results of a well-powered placebo- and positive- controlled trial investigating the effect of a supratherapeutic dose of tadalafil (100 mg) on QT interval. The dose used exceeded the Cmax achieved under any of the following scenarios: at steady state, upon coadministration with the potent CYP 3A inhibitors ketoconazole (400 mg QD) and ritonavir (200 mg BID), in mild and moderate renal impairment, or in patients with End Stage Renal Failure receiving hemodialysis. The results of this study suggest that there is a small (3-5 msec increase) and, possibly, clinically insignificant effect of tadalafil on QT interval.

IV. Question Based Review

1. Is there a need for a 5 mg dose?

The original reviewer of NDA 21-368 noted that systemic tadalafil exposure was approximately 2-fold higher in subjects with mild and moderate renal impairment following administration of 10 mg tadalafil. A single 10 mg dose of tadalafil was well tolerated in healthy subjects and subjects with mild renal impairment, but was not well tolerated in subjects with moderate renal dysfunction, prompting dose reduction to 5 mg. The onset of adverse events—primarily back pain and myalgia—generally occurred 20 hours after peak plasma concentrations of tadalafil, when tadalafil's methylcatechol glucuronide metabolite concentrations were high. Renal impairment has a greater effect on the disposition of tadalafil's methylcatechol glucuronide metabolite than on the parent compound, as expected for a renally-cleared metabolite.

In evaluating the need for a 5 mg dose, the primary focus was on the pharmacokinetic and safety data from the following three studies.

(1) Study LVDT: A Study to Investigate the Tolerability and Pharmacokinetics of IC351 (tadalafil) in Subjects on Hemodialysis for Renal Failure

> An open-label study in 16 male or female subjects, 25-75 years of age, with End Stage Renal Failure (ESRF) who were receiving three hemodialysis sessions per week. Single doses of 5, 10 or 20 mg tadalafil were administered approximately 24 to 30 hours prior to each subject's first hemodialysis session in the study period.

(2) Study LVAJ: A Comparative Study on the Pharmacokinetics, Safety and Tolerability of IC351 (tadalafil), Following a Single Oral Dose in Patients with Mild, Moderate or Severe Renal Dysfunction and Healthy Subjects

An open-label study of single oral doses of 5 and 10 mg tadalafil in a total of 12 healthy subjects (8 receiving 10 mg, 4 receiving 5 mg), 8 patients with mild renal impairment (5 receiving 10 mg, 3 receiving 5 mg) and 12 patients with moderate renal impairment (6 receiving 10 mg, 6 receiving 5 mg).

(3) Study LVBX: A Study in Healthy Subjects to Determine the Relative Bioequivalence of Three Tablet Strengths (4 x 2.5mg vs 2 x 5 mg vs 1 x 10 mg) of Tadalafil and the Dose Proportionality of Tadalafil Pharmacokinetics when Administered at Four Dose Levels (2.5, 5, 10 and 20 mg)

A two-part bioequivalence and dose-proportionality study in 24 and 16 healthy subjects, respectively.

Note that Study LVAJ and Study LVBX were reviewed in the original submission of the tadalafil NDA, while Study LVDT was provided in the May 27, 2003 resubmission. In this review, the data from healthy subjects in Study LVBX and Study LVAJ serve as a comparator arm for the parameters in Study LVDT. Such a comparator arm is necessary since Study LVDT did not include healthy subjects.

The results of Study LVDT suggest that End Stage Renal Failure has a greater impact on metabolite (Total IC710) disposition than on the parent compound. This is reasonable given that the metabolites are primarily renally cleared. Relative to healthy subjects in studies LVAJ or LVBX, subjects with ESRF receiving a 5 mg tadalafil dose had no change in mean tadalafil AUC, a 23% decrease in mean tadalafil Cmax, a 2.7–fold increase in mean Total IC710 AUC, and a 1.6–fold increase in mean Total IC710 Cmax. Subjects receiving 10 mg tadalafil had between 1.1-fold to 4.8-fold increases in mean tadalafil AUC, between zero to 2.2-fold increases in mean tadalafil Cmax, 2.1 to 3.3-fold increases in Total IC710 AUC, and 1.3 to 1.8-fold increases in mean Total IC710 Cmax. Subjects receiving 20 mg tadalafil had a 2.7-fold and 1.9-fold increase in tadalafil AUC and Cmax, respectively.

The following table shows that the disposition of tadalafil and Total IC710 differed between subjects with ESRF versus subjects with mild and moderate renal impairment. For the 10 mg tadalafil dose, median tadalafil Tmax in ESRF (2 to 4 hours) was greater than that in mild (2 hours) and moderate (2 hours) renal impairment and in healthy subjects (1 to 2 hours). Median tadalafil t½ in ESRF (15.2 to 24.8 hours) was between that in mild and moderate renal failure (22 to 26 hours) and healthy subjects (14 to 17.6 hours). Median Total IC710 tmax in ESRF (52.4 to 77.5 hours) was greater than that in mild (36 hours) and moderate (48 hours) renal failure and in healthy subjects (18 hours).

10 mg Tadalafil
(Geometric Mean and CV%)

	Healthy Subjects (N=15) Study LVBX (B)	Healthy Subjects (N=24) Study LVBX (A)	Healthy Subjects (N=8) Study LVAJ	Mild Renal Impair (N=3) Study LVAJ	Moderate Renal Impair (N=6) Study LVAJ	End Stage Renal Failure (N=12*) Study LVDT	
						*Poland N=6	*UK N=6
AUC Tadal	3647 (34.0)	4005 (34.2)	2868 (44.2)	6280 (46.1)	4911 (50.1)	4023 (38.2)	13749 (36.7)
Cmax Tadal	190 (21.7)	184 (24.3)	183 (31.2)	217 (21.0)	220 (22.2)	186 (17.2)	394 (20.8)
t½ Tadal	16.7 (34.4)	17.6 (27.8)	14 (45.8)	26 (32.7)	22 (43.0)	15.2 (41.6)	24.8 (37.9)
tmax Tadal	2.0	2.0	1.0	2.0	2.0	4.0	2.04
AUC Total IC710			4823 (66.7)	12657 (35.3)	17502 (45.1)	9983 (28.5)	15891 (34.8)
Cmax Total IC710			86.5 (53.4)	113 (43.7)	142 (26.3)	109 (35.6)	158 (33.5)
t½ Total IC710			20.0 (30.7)	44.3 (19.5)	55.4 (45.9)	NA	NA
tmax Total IC710			18.0	36.0	48.0	52.4	77.5

Tadalafil and Total IC710 (metabolite) Parameters Estimated in Study LVBX, LVAJ, and LVDT for the 10 mg Tadalafil Dose. All values are reported as mean (CV%) except for tmax which is median (min,max).

In this study, hemodialysis occurred 24-30 hours after subjects received their single dose of tadalafil. The ratio of post-dialysis to pre-dialysis concentrations of tadalafil and its metabolite was reported as 0.9 (90% confidence interval=0.85,0.96) and 1.18 (90% confidence interval=1.11,1.25), respectively. The sponsor claims that hemodialysis contributes negligibly to the elimination of either tadalafil or its methylcatechol glucoronide. It is unknown whether hemodialysis would have had a more significant impact on exposure had it occurred sooner after tadalafil dosing.

Mean protein binding of tadalafil in ESRF subjects undergoing hemodialysis was reported as 96%, thus, 4% of drug is unbound. In healthy subjects, mean protein binding was reported as 94%, thus, 6% is unbound. The sponsor reported that this 33% reduction in protein binding (fraction unbound) did not appear to be different between pre- and

post- dose, or between the 10 and 20 mg dose groups and that this was not a factor explaining the difference in disposition for the groups.

There was a greater than dose proportional increase in tadalafil's AUC and Cmax in ESRF for an increase in dose from 5 mg to 20 mg. An 11.1-fold and 7.9-fold increase in tadalafil's AUC and Cmax, respectively, were observed with this 4-fold increase in dose. There was a greater than dose proportional increase in tadalafil's AUC and Cmax observed for one cohort receiving 10 mg relative to the 5 mg dose, as well. An 8.4-fold increase in AUC and a 5-fold increase in Cmax was observed with this 2-fold increase in dose. In healthy subjects, AUC increases in a dose proportional manner across the 5 to 20 mg dose range while Cmax increases in a slightly *less* than dose proportional manner across the 10 to 20 mg dose range.

The following table summarizes the adverse events observed by severity. There were no drug-related adverse events observed in the six (6) subjects with ESRF receiving 5 mg tadalafil. Thirty-three (33) percent of the twelve (12) subjects receiving the 10 mg dose experienced primarily mild adverse events. Approximately 17% of the 6 subjects receiving 20 mg tadalafil experienced drug-related adverse events—one reported dizziness and one reported feeling hot. Headache and somnolence were the major adverse events reported. No episodes of myalgia or back pain were reported during the study.

Treatment	Number of subjects studied	Subjects [n (%)] with adverse events (all causalities)	Number of adverse events and severity (all causalities)	Subjects [n (%)] with adverse events (drug-related[a])	Number of adverse events and severity (drug-related[a])
5 mg IC351	6	3 [50.0%]	Mild 2 Moderate 1 Severe 0 Total 3	0 [0.0%]	Mild 0 Moderate 0 Severe 0 Total 0
10 mg IC351	12	5 [41.7%]	Mild 6 Moderate 1 Severe 0 Total 7	4 [33.3%]	Mild 5 Moderate 1 Severe 0 Total 6
20 mg IC351	6	1 [16.7%]	Mild 2 Moderate 0 Severe 0 Total 2	1 [16.7%]	Mild 2 Moderate 0 Severe 0 Total 2

Source: Section 14.3.4 (Table 1)

[a] Adverse events considered to be possibly related to IC351

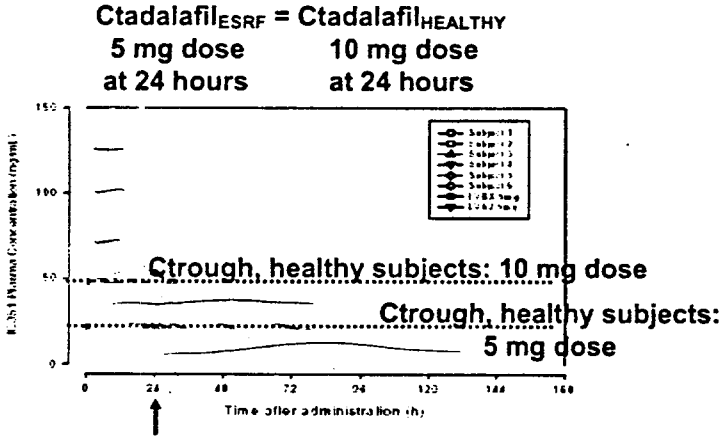
Summary of Treatment-Emergent Adverse Events in Study LVDT.

Given that ESRF subjects undergoing hemodialysis receiving 10 mg tadalafil had between 1.1-fold to 4.8-fold increases in mean tadalafil AUC, between zero to 2.2-fold increases in mean tadalafil Cmax, 2.1 to 3.3-fold increases in Total IC710 AUC, and 1.3 to 1.8-fold increases in mean Total IC710 Cmax, a 5 mg dose is recommended as a daily dose. A 5 mg tadalafil dose is recommended in subjects with moderate renal impairment, as well, given that the 10 mg dose was poorly tolerated in a study on subjects with moderate renal impairment and prompted a dose reduction to 5 mg. Although there were

few adverse events observed in subjects with ESRF receiving the 10 mg dose, the sample size was not large enough to rule out the possibility.

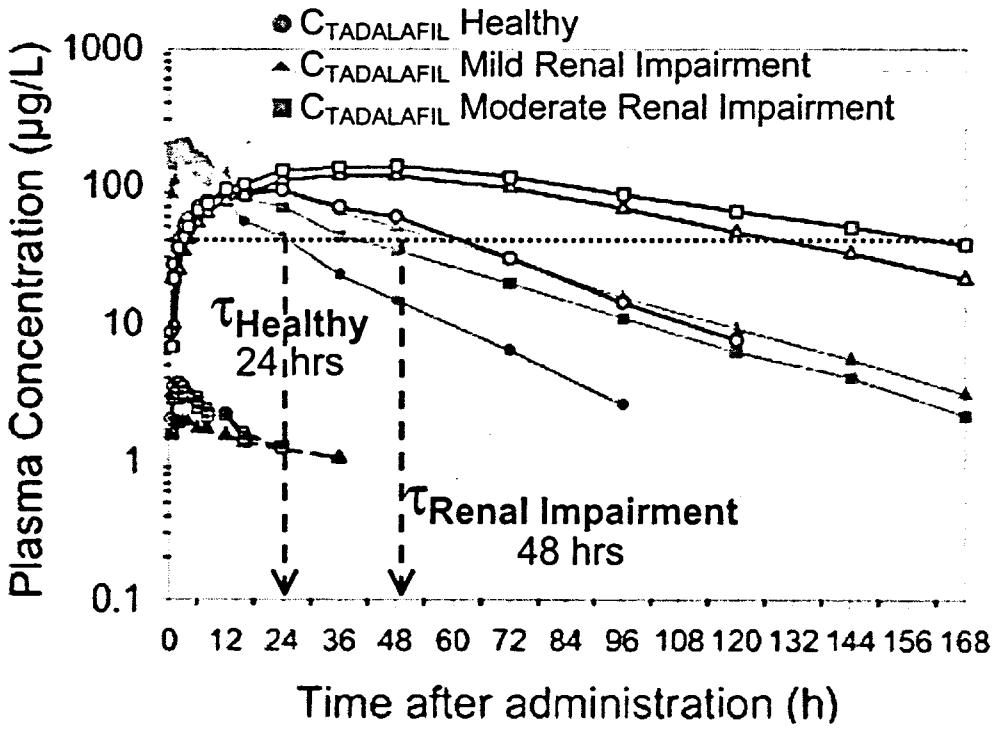
If a 10 mg dose of tadalafil is to be used in renally impaired subjects, the dosing interval should be adjusted. The recommended dosing interval is based on finding the time after dosing at which the trough level in renally impaired subjects is equivalent to the trough level (concentration at 24 hours post-dose) in healthy subjects. Since Study LVDT is a single dose study, the trough levels in this study will be compared to trough levels from single dose studies in healthy volunteers.

The following figure shows the mean concentration-time profile from two studies in which healthy subjects received a 5 mg tadalafil dose (Study LVBX and Study LVAJ) and the individual concentration-time profiles for each subject with ESRF in Study LVDT that received 5 mg tadalafil. Note that the mean trough level (concentration at 24 hours) in healthy subjects for the 5 mg dose is not achieved by all ESRF subjects until 72 hours post-dose. The tadalafil concentration in the majority of ESRF subjects 24 hours after a 5 mg dose are equivalent to trough levels after administering 10 mg tadalafil to healthy subjects. Thus, 5 mg tadalafil may be dosed to subjects with ESRF every 24 hours. If 10 mg is used, it should be dosed at most once every 72 hours.



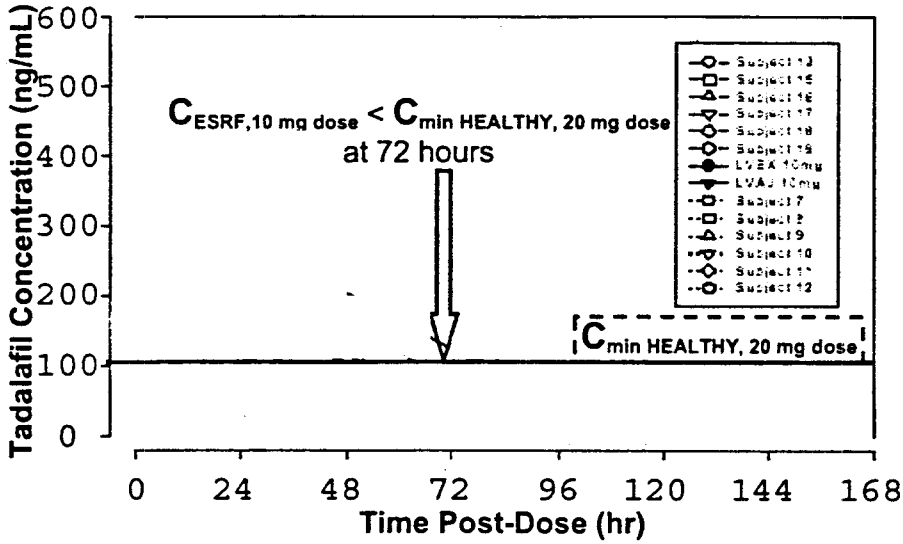
Plasma Concentrations of Tadalafil (IC351) versus Time Following a Single Oral 5 mg Tadalafil Dose to End-Stage Renal Failure Subjects Undergoing Hemodialysis (Study LVDT) and Healthy Subjects (Study LVBX and Study LVAJ).

The following figure shows the plasma concentration-time profile for tadalafil and its metabolites after 10 mg is dosed to renally impaired and healthy subjects. The superimposed line highlights the trough concentration for healthy subjects. The plasma concentration 24 hours post-dose in healthy subjects corresponds to the concentration observed at 48 hours in renally impaired subjects. Thus, the potential dosing interval for a 10 mg dose in mild and moderate renal impairment is at most once every 48 hours.



Plot to Estimate the Dosing Interval in Subjects with Mild and Moderate Renal Impairment. The plasma concentration 24 hours post-dose of 10 mg tadalafil in healthy subjects corresponds to the concentration at 48 hours in renally impaired subjects. Thus, the recommended dosing interval in mild and moderate renal impairment is at most once every 48 hours.

The following figure shows the individual plasma concentration-time profiles for tadalafil in 12 patients with End Stage Renal Failure Undergoing Dialysis receiving 10 mg tadalafil. The plot of the mean concentration for healthy subjects receiving a 10 mg tadalafil dose is provided on the plot, as well (line labeled: Study LVBX and Study LVAJ). The horizontal line on the plot indicates the trough concentration for a 20 mg dose of tadalafil in healthy subjects. The 20 mg trough level was selected as it represents the minimum concentration for the highest proposed dose. The plasma concentration 24 hours post-dose in healthy subjects for the 20 mg dose corresponds to the concentration at 72 hours in patients with ESRF. This plot highlights the excessive time at which ESRF subjects have exposure to drug if 10 mg is dosed.



Plot to Estimate the Dosing Interval in Subjects with End Stage Renal Failure Undergoing Dialysis.

Note that tadalafil was not studied in ESRF subjects who were not undergoing dialysis, but dialysis appeared to contribute little to tadalafil elimination when performed 24-30 hours post-dose.

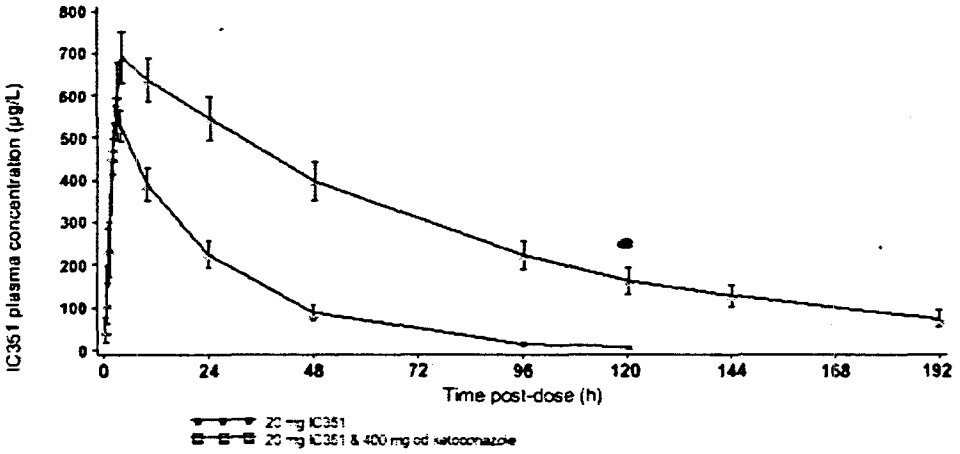
2. What is the significance of the drug-drug interaction between tadalafil and the CYP 3A4 inhibitors ketoconazole and ritonavir?

The reviewer of the initial submission of the tadalafil NDA noted that tadalafil exposure was increased by 107% when co-administered with 200 mg ketoconazole and predicted higher exposures with 400 mg ketoconazole, protease inhibitors (such as ritonavir and saquinavir), other CYP3A4 inhibitors (such as erythromycin and itraconazole), and grapefruit juice. A pharmacokinetic interaction study of tadalafil (single dose of 20 mg) with ritonavir (500 mg bid) at steady state was recommended in the review.

The sponsor submitted the results of Study LVEV: A Study to Assess the Effect of Ritonavir and Ketoconazole on the Pharmacokinetics of 20 mg IC351 (Tadalafil) in Healthy Subjects. Study LVEV was a randomized, open-label study conducted in two parts. Part A examined the interaction of tadalafil with two dose levels of ritonavir (200 mg and 600 mg BID) and Part B examined the interaction of tadalafil with ketoconazole (400 mg QD). In each of Part A and Part B, tadalafil 20 mg was dosed alone in Period 1. In Period 2, CYP 3A4 inhibitor dosing started on study Day 1 and continued until Day 10, with tadalafil 20 mg dosing beginning two days after the start of CYP 3A4 inhibitor dosing (Study Day 3). Eight (N=8) subjects were assigned to each ritonavir study arm and twelve (12) subjects were assigned to ketoconazole.

The results of Study LVEV suggest that coadministration of 20 mg tadalafil with 400 mg QD ketoconazole causes the most significant CYP 3A4 drug-drug interaction with respect to increase in tadalafil exposure. In this case, $AUC_{0\rightarrow\infty}$ increased 4.1-fold on average and the most extreme change was 5.9-fold. In addition, Cmax increased 1.2-fold

on average and the most extreme change was 1.9-fold. The following figure shows the concentration-time profiles for tadalafil dosed with and without ketoconazole.



Arithmetic Mean (±SEM) Plasma Concentration-Time Profiles of Tadalafil (IC351) Following Oral Administration of a Single 20 mg Dose Alone (N=12) and in Combination with 400 mg QD Ketoconazole (N=12). The top curve is the profile from the drug interaction study. The bottom curve is from tadalafil dosing alone.

The sponsor performed a drug-drug interaction study with 600 mg BID ritonavir, but the results are inconclusive because the 600 mg BID ritonavir dose was poorly tolerated. Five of the 8 subjects were withdrawn after receiving 600 mg BID ritonavir but prior to receiving a coadministered dose of tadalafil. Only 3 of the 8 subjects receiving 600 mg BID ritonavir remained in the study until the first coadministered tadalafil dose on Day 3, but discontinued after Day 3 because of ritonavir-related adverse events. The following figure shows the concentration-time profiles from the ritonavir interaction studies. Administration of 200 mg BID ritonavir resulted in a mean 2.6-fold increase in AUC and no change in mean Cmax.

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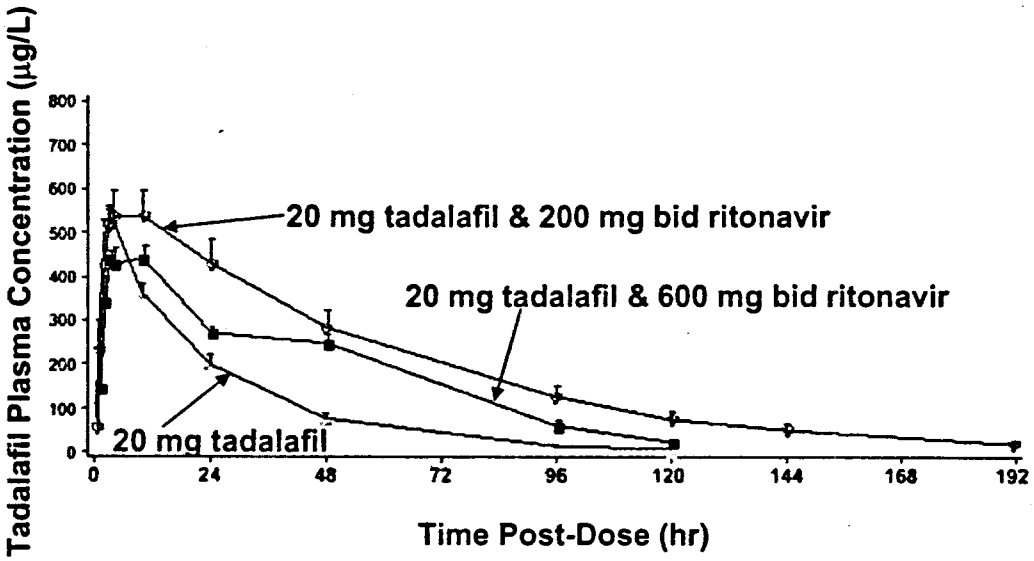


Arithmetic Mean (±SEM) Plasma Concentration-Time Profiles of Tadalafil Following Oral Administration of a Single 20 mg Dose Alone (N=16) and in Combination with 200 mg BID Ritonavir (N=8) or 600 mg BID. Ritonavir (N=3).

Despite the lack of data on the interaction between 600 mg BID ritonavir and 20 mg tadalafil, the sponsor asserted that the "worst case scenario" for potent CYP 3A inhibition is that ritonavir 600 mg BID increases tadalafil exposure to a similar extent as 400 mg ketoconazole QD. Several pieces of evidence were provided to support this hypothesis. Evidence included:

(1) Long term administration of high dose ritonavir has been associated with a reduction in its own exposure due to induction of CYP 3A. Therefore, the inhibitory effect of ritonavir may decrease with time and dose.
(2) The effect of ritonavir on Cmax is relatively small for most compounds.
(3) Ritonavir is known to inhibit multiple drug-metabolizing enzymes, including CYP 3A, CYP 2D6, and CYP 2C. A significant component of its inhibitory effect is due to inhibition of first-pass metabolism. Tadalafil is a low clearance drug (apparent oral clearance = 2.48 L/hr). Moderate to high clearance drugs are more susceptible to effects of strong inhibitors on first-pass and systemic metabolism than low clearance drugs.
(4) *In vitro* concentration-response data has shown that ritonavir is nearly as potent as ketoconazole for CYP 3A inhibition

By means of simulations using the same study design, sample size, and sampling strategy, the sponsor replicated Study LVEV 200 times to characterize the expected distribution of possible AUC outcomes. The simulation model accounted for inhibition of first-pass metabolism as well as effects on systemic clearance of tadalafil. Worst-case assumptions for the influence of key model parameters—such as the effect on first-pass and the influence of ritonavir on inhibitory constant and protein binding were tested within the simulation environment. The median predicted tadalafil AUC ratio in the presence and absence of 200 mg BID ritonavir was 2.2—the same value as reported in

Study LVEV. The median and maximum AUC ratios predicted in the presence versus absence of 600 mg BID ritonavir were 3.3 and 4.0, respectively. This inhibitory response is slightly less than that for ketoconazole 400 mg/day.

The following table summarizes the relative change in parameters for tadalafil when dosed with the CYP 3A inhibitors tested in this study.

	Ketoconazole 400 mg QD (N=)	Ritonavir 200 mg BID (N=8)	Ritonavir 600 mg BID (N=3)
Cmax	↑ 1.2-fold	No change	↓ 16%
AUC	↑ 4.1-fold	↑ 2.2-fold	↑ 1.7-fold
tmax	3.03 hours* 1 hour***	3.00 hours* 1 hour***	7 hours***
t½	35 hours**	15.5 hours**	0.8 hours**
CL/F	↓ 76%	↓ 60%	↓ 40%
Vz/F	↓ 22%	↓ 20%	↓ 40%

*Median difference in tmax for tadalafil + CYP 3A inhibitor versus tadalafil alone
**Difference between geometric mean t½ for Tadalafil + CYP 3A inhibitor versus tadalafil alone.
***Difference between median tmax for Tadalafil + CYP 3A inhibitor versus tadalafil alone.

Relative Change in Tadalafil Pharmacokinetic Parameters for the CYP 3A Interaction Studies Relative to Dosing Tadalafil Alone.

Coadministration of 20 mg tadalafil with 400 mg QD ketoconazole reduced the geometric mean CL/F for tadalafil by 76%. The AUC and Cmax of tadalafil's major metabolite, a methylcatechol glucuronide, was lower after coadministration with ketoconazole (25% decrease in AUC, 62% decrease in Cmax) or ritonavir (200 mg BID regimen: 66% decrease in AUC, 80% decrease in Cmax) relative to dosing tadalafil alone.

The following chart reports the incidences of adverse events in this study. The highest levels of tadalafil exposure (obtained upon dosing 20 mg tadalafil with 400 mg ketoconazole) was not associated with the highest incidence of AEs. Back pain was frequently reported, with 42.8%, 37.5%, and 25% of subjects receiving 20 mg tadalafil alone, 20 mg tadalafil + 200 mg BID ritonavir, and 20 mg tadalafil + 400 mg QD ketoconazole reporting back ache, respectively. Myalgia was reported by 2/28 (7.1%), 1/8 (12.5%), and 1/12 (8.3%) of subjects receiving 20 mg tadalafil alone, 20 mg tadalafil + 200 mg BID ritonavir, and 20 mg tadalafil + 400 mg ketoconazole, respectively. The incidence of adverse events is consistent with the hypothesis that both drug and metabolite concentrations may be the cause. Although tadalafil levels increased with CYP 3A4 inhibition, metabolite levels decreased with increased CYP 3A4 inhibition and 400 mg ketoconazole + 20 mg tadalafil yielded fewer adverse events than 20 mg tadalafil alone.

MedDRA term	20 mg IC351 (N=28)	20 mg IC351 & 200 mg b.d. ritonavir (N=8)	20 mg IC351 & 600 mg b.d. ritonavir (N=8[a])	20 mg IC351 & 400 mg o.d. ketoconazole (N=12)
	Number of adverse events [number of subjects with adverse event]			
Headache NOS	19 [16]	2 [2]	3 [1]	18 [9]
Back pain	15 [12]	3 [3]		6 [3]
Myalgia	3 [2]		1 [1]	1 [1]
Muscle cramps	2 [1]			2 [1]
Arthralgia	2 [2]			1 [1]
Feeling hot			1 [1]	1 [1]
Musculoskeletal stiffness	2 [2]			
Lethargy		2 [2]		
Nasal congestion	1 [1]	1 [1]		
Sensation of pressure NOS				2 [1]
Back stiffness	1 [1]			
Dyspepsia				1 [1]
Eye pain	1 [1]			
Flushing	1 [1]			
Limb discomfort NOS	1 [1]			
Nausea	1 [1]			
Neck stiffness	1 [1]			
Pain in limb		1 [1]		
Somnolence	1 [1]			
Total	**51 [21]**	**9 [6]**	**5 [2]**	**32 [10]**

Source: Section 14.3.4 (Table 2.2)

N= Number of subjects

Adverse events presented were treatment-emergent with respect to dosing with IC351

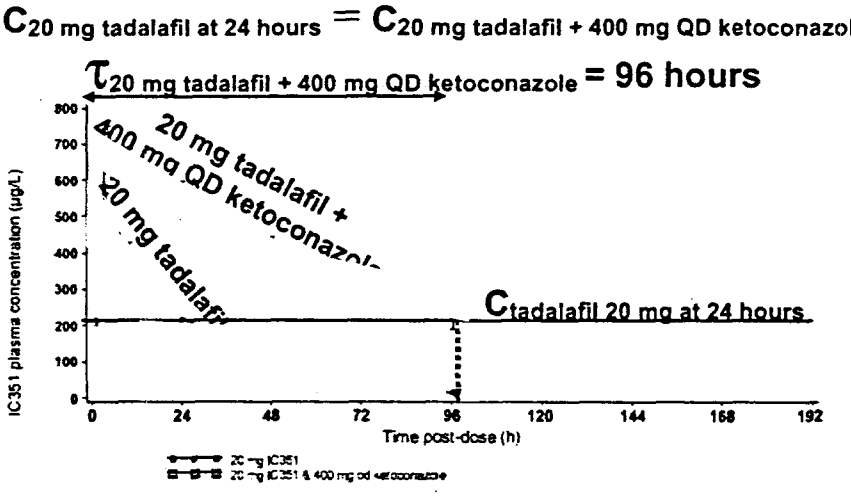
[a] Three subjects received IC351

NOS = Not otherwise specified

Frequency of Treatment-Emergent Drug-Related Adverse Events in Study LVEV by Type.

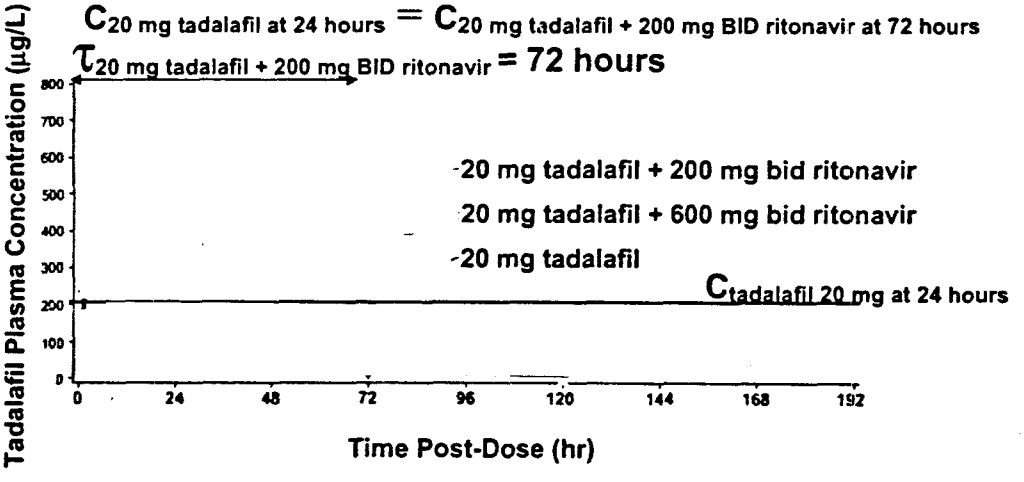
The recommendation based on these results is that subjects taking potent CYP 3A inhibitors—such as ketoconazole and ritonavir—should be restricted to a 10 mg dose of tadalafil.

The following plot highlights the excessive exposure to drug expected if a 20 mg dose is used in subjects taking 400 mg ketoconazole QD. The horizontal line on the following plot of the concentration-time profile for subjects receiving 20 mg tadalafil alone and with 400 mg ketoconazole QD indicates the trough concentration (concentration at 24 hours post-dose) for a 20 mg dose of tadalafil. The plasma concentration 24 hours post-dose after 20 mg tadalafil is dosed alone corresponds to the concentration at 96 hours when 20 mg tadalafil is coadministered with 400 mg ketoconazole QD. Note that this trough level is higher than in the plot used to estimate the dosing interval in renal impairment. The renal impairment studies were single-dose studies.



Graphical Approach to Estimating the Dosing Interval in Subjects Taking 20 mg tadalafil with 400 mg QD Ketoconazole.

Similar to the previous plot, the following plot highlights the excessive exposure to drug expected if a 20 mg dose is used in subjects taking 200 mg ritonavir BID. The horizontal line on the following plot of the concentration-time profile for subjects receiving 20 mg tadalafil alone and with 200 mg ritonavir BID indicates the trough concentration (concentration at 24 hours post-dose) for a 20 mg dose of tadalafil. The plasma concentration 24 hours post-dose corresponds to the concentration at 72 hours in subjects taking 200 mg ritonavir BID. Thus, the recommended dosing interval in this situation is 72 hours. Note that this trough level is higher than in the plot used to estimate the dosing interval in renal impairment. The renal impairment studies were single-dose studies.



Graphical Approach to Estimating the Dosing Interval in Subjects Taking 20 mg tadalafil with 200 mg BID Ritonavir.

There are no pharmacokinetic data available regarding the interaction of a 10 mg tadalafil dose with either 400 mg ketoconazole QD or 200 mg ritonavir BID. The data from the

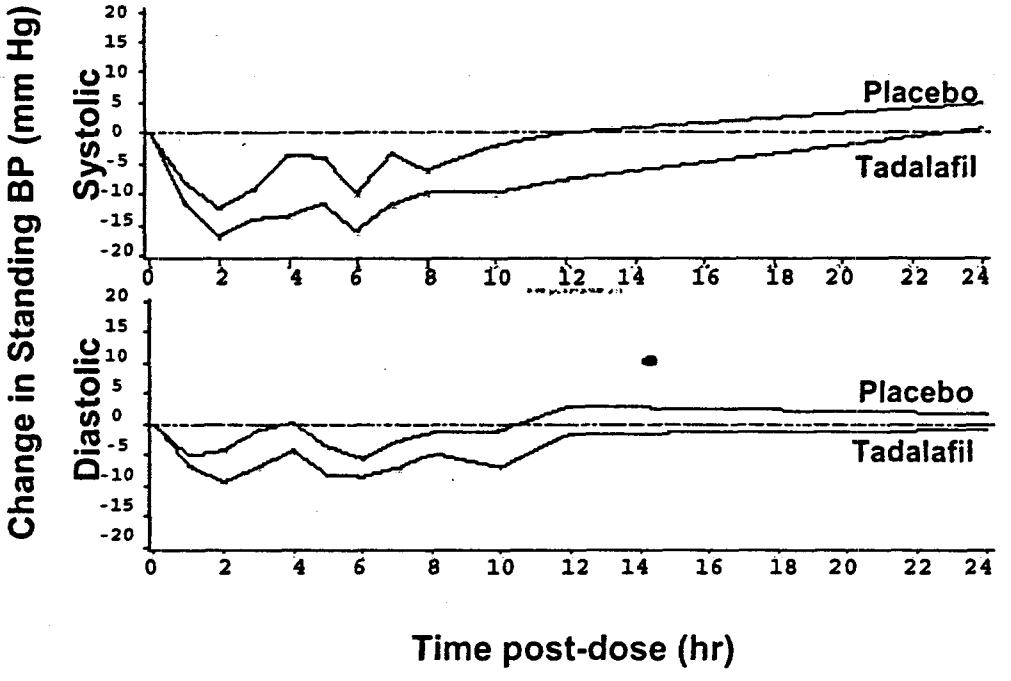
studies of 20 mg tadalafil with these potent CYP 3A inhibitors can be used to infer an appropriate dosing regimen for a 10 mg dose. Given that tadalafil has linear kinetics for 10 and 20 mg doses, one can halve the concentrations at each time point in the 20 mg study to predict the level expected for the 10 mg dose. If this approach is taken, the previous two plots suggest that a 10 mg dose of tadalafil coadministered with 400 mg QD ketoconazole is expected to fall below the trough (24 hour post-dose) concentration of 20 mg tadalafil 72 hours post-dose. Thus, the recommended dosing interval with potent CYP 3A inhibitors is 10 mg at most once every 72 hours.

3. What is the clinical significance of the interaction with doxazosin?
Given that both tadalafil and alpha adrenergic antagonists used in the treatment of benign prostatic hypertrophy (BPH) exert pressor effects and that patients with BPH might also suffer erectile dysfunction, it was necessary to investigate the interaction between tadalafil and drugs from this class of compounds. The approvable letter requested that the sponsor provide information to support labeling regarding the interaction of 20 mg Cialis with doxazosin or terazosin in doses used to treat symptoms of benign prostatic hypertrophy. In a previous study performed in healthy subjects (Study LVAY), no evidence of a significant pharmacodynamic effect on blood pressure was demonstrated when the alpha-1A adrenergic antagonist tamsulosin, or FLOMAX®, at a dose of 0.4 mg once-daily was co-administered with tadalafil at 10 mg or 20 mg doses.

To address this issue, the sponsor submitted the results of Study LVFG: A Pharmacodynamic Study to Evaluate the Interaction Between 20 mg IC351 (Tadalafil) and 8 mg QD Doxazosin, an Alpha 1 Adrenergic Antagonist, in Healthy Male Subjects. The antagonist used in the present study was doxazosin, or CARDURA®—a drug which is less selective for alpha receptors in the prostate than tamsulosin. In this study, doxazosin was administered at a dose of 8 mg once-daily, which is its highest approved oral dose. Doxazosin is marketed in 1 mg, 2 mg, 4 mg, and 8 mg tablets.

This was a double-blind, placebo-controlled, randomized, two-period crossover study with a 10 day washout period investigating the effect of a single 20 mg tadalafil dose on blood pressure after once-daily dosing (QD) of 8 mg doxazosin for 7 days. The study was conducted in 18 healthy males aged 40-70 years. The primary endpoint was maximal post-baseline drop in standing systolic blood pressure. The terminal elimination half life for doxazosin is 22 hours. Steady state with relatively small changes in peak to trough concentrations is expected after 7 days of daily dosing. Doxazosin and tadalafil were dosed simultaneously on the concomitant dosing day in this study with the aim of simultaneously achieving peak concentration for both drugs. This was appropriate given that (according to labeling), peak plasma levels of doxazosin occur 2-3 hours post-dose and median tadalafil tmax is 2 hours.

The following figure shows the results with respect to the primary endpoint (change in standing systolic blood pressure) and change in standing diastolic blood pressure.



Mean Changes from Baseline in Standing Blood Pressure.

In Study LVFG, mean change in standing blood pressure was greater for tadalafil compared to placebo at all time points. The mean change in standing systolic blood pressure returned to baseline at 24 hours after tadalafil administration compared to 12 hours post placebo dosing.

The following table of the statistical analysis of the study shows that based upon the primary endpoint of maximal post-baseline drop in standing systolic blood pressure, there was a significant difference (with 95% confidence; upper limit of confidence interval: 15.5 mmHg) observed between subjects receiving the tadalafil + doxazosin regimen versus the placebo + doxazosin regimen. The mean difference between the two treatment arms was 9.81 mmHg—greater than the preset criteria of 8 mmHg. The maximum mean drop in standing systolic blood pressure occurred at 2 hours and 6 hours post dose.

Parameter	LS mean: 20 mg IC351 & 8 mg q.d. doxazosin	LS mean: Placebo & 8 mg q.d. doxazosin	Mean difference[a]	95% confidence limits for the mean difference
Maximal post-baseline drop in standing systolic blood pressure (mmHg)	27.8	17.9	9.81	4.11, 15.5
Maximal post-baseline drop in standing diastolic blood pressure (mmHg)	14.4	9.11	5.33	0.618, 10.0
Maximal post-baseline increase in standing heart rate (bpm)	**16.1**	**12.3**	**3.83**	**0.480, 7.19**

Source: Section 14.2.3 (Table 1)
[a] IC351 & doxazosin – placebo & doxazosin

Statistical Analysis of Derived Parameters for Standing Vital Signs.

The following table reports the response with respect to outlying values. The percentage of subjects with potentially clinically significant decreases from baseline in standing systolic blood pressure when 20 mg tadalafil was co-administered with doxazosin (28%) was greater than when placebo was co-administered with doxazosin (11%). In terms of absolute values, five out of 18 subjects (28%) had standing systolic blood pressure less than 85 mmHg following dosing with tadalafil, compared to one out of 18 subjects (6%) following dosing with placebo.

Criteria	20 mg IC351 & 8 mg q.d. doxazosin (N=18)	Placebo & 8 mg q.d. doxazosin (N=18)
Standing systolic blood pressure <85 mmHg	5 [28]	1 [6]
Standing diastolic blood pressure <45 mmHg	1 [6]	0 [0]
Supine systolic blood pressure <85 mmHg	0 [0]	1 [6]
Supine diastolic blood pressure <45 mmHg	0 [0]	0 [0]
Change from baseline in standing SBP >30 mmHg	5 [28]	2 [11]
Change from baseline in standing DBP >20 mmHg	2 [11]	1 [6]
Change from baseline in supine SBP >30 mmHg	1 [6]	1 [6]
Change from baseline in supine DBP >20 mmHg	2 [11]	0 [0]

Source: Section 14.2.3 (Table 3)

Number of Subjects [% Subjects] with Potentially Clinically Significant Blood Pressure Effects.

The following two tables report the incidence of adverse events. Two-thirds (66.7%) of subjects receiving tadalafil experienced a drug-related adverse event compared to 38.9% receiving placebo, with more severe and moderate events occurring in subjects receiving tadalafil than placebo. There were 2 versus zero incidences of severe drug-related adverse events for subjects receiving tadalafil compared to subjects receiving placebo, respectively. There were 6 versus 2 incidences of moderate drug-related adverse events for subjects receiving tadalafil compared to subjects receiving placebo, respectively.

Treatment	Subjects [%] with adverse events (all causalities)	Number of adverse events and severity (all causalities)		Subjects [%] with adverse events (drug-related[a])	Number of adverse events and severity (drug-related[a])	
20 mg IC351 & 8 mg q.d. doxazosin (N=18)	12 [66.7%]	Mild	30	12 [66.7%]	Mild	20
		Moderate	9		Moderate	6
		Severe	2		Severe	2
		Total	41		Total	28
Placebo & 8 mg q.d. doxazosin (N=18)	10 [55.6%]	Mild	24	7 [38.9%]	Mild	12
		Moderate	4		Moderate	2
		Severe	0		Severe	0
		Total	28		Total	14

Source: Section 14.3.4 (Table 1.1)

N = Number of subjects studied

Adverse events summarised were treatment-emergent with respect to dosing with study drug on Day 1

a Adverse events considered to be possibly related to IC351 or placebo

Summary of Treatment-Emergent Adverse Events.

The following table reports the breakdown of adverse events by type. Six out of 18 (33.3%) subjects receiving tadalafil experienced back pain compared to zero subjects receiving placebo. Three out of 18 (16.7%) subjects receiving tadalafil experienced dizziness compared to zero subjects receiving placebo. Two out of 18 (11.1%) subjects receiving tadalafil experienced myalgia compared to zero subjects receiving placebo. One subject receiving tadalafil out of 18 experienced chest pain compared to zero receiving placebo. One out of 18 subjects receiving tadalafil experienced each of the following adverse events compared to zero subjects receiving placebo: arthralgia, asthenia, chest pain, dry mouth, nausea, pain in limb.

	Number of adverse events [number of subjects with adverse event]	
MedDRA term	20 mg IC351 & 8 mg q.d. doxazosin (N=18)	Placebo & 8 mg q.d. doxazosin (N=18)
Back pain	6 [6]	
Headache NOS	5 [4]	6 [5]
Somnolence	4[4]	5 [5]
Dizziness	3 [3]	
Myalgia	2 [2]	
Fatigue	1 [1]	1 [1]
Vertigo	1 [1]	1 [1]
Arthralgia	1 [1]	
Asthenia	1 [1]	
Chest pain	1 [1]	
Dry mouth	1 [1]	
Dyspepsia		1 [1]
Nausea	1 [1]	
Pain in limb	1 [1]	
Total	**28 [12]**	**14 [7]**

Source: Section 14.3.4 (Table 2.2)

NOS = Not otherwise specified

Frequency of Treatment-Emergent Study Drug-Related Adverse Events by Type.

The onset of back pain and myalgia following administration of tadalafil occurred between 10 and 40 hours after dosing with tadalafil. The duration of back pain was long for 3 subjects—lasting approximately 3 to 7 days. The number of subjects experiencing headache, somnolence, fatigue, and vertigo was equivalent after administration of tadalafil and placebo. There was a difference in the duration of the episode of vertigo on tadalafil versus on placebo.

Given the clinically significant interaction between doxazosin and tadalafil, the use of these drugs in combination should be contraindicated. The sponsor may choose to investigate the interaction between tadalafil and lower doses of doxazosin.

The results and design of the sponsor's interaction study with tamsulosin was reevaluated. This study of tamsulosin with 10 mg and 20 mg tadalafil doses was a placebo-controlled, randomized, three-period crossover study designed to compare the pharmacodynamic effects of tadalafil and placebo when co-administered with tamsulosin. In each of three treatment periods, subjects were administered single oral doses of either 10 mg tadalafil, 20 mg tadalafil or placebo 2 hours after receiving a daily tamsulosin dose (0.4 mg). Subjects began tamsulosin dosing 7 days prior to the single dose of tadalafil or placebo and received tamsulosin until the day after the dose of tadalafil or placebo was administered. The tamsulosin label reports that steady state concentrations of tamsulosin are achieved by the fifth day of once-daily dosing.

In this study, subjects received tamsulosin in the fasted state. Tamsulosin labeling reports that maximum tamsulosin concentrations for the 0.4 mg QD regimen occurs 4 to 5 hours post-dosing in the fasted state. Tmax for tadalafil occurs at a median of 2 hours post-dose. Thus, it was appropriate for the sponsor to dose tamsulosin 2 hours after subjects received tadalafil in order to have the peak concentration for both drugs occur simultaneously.

Tamsulosin caused a difference in maximum standing systolic blood pressure of -4 mmHg and -4 mmHg when dosed with 10 and 20 mg tadalafil, respectively, and a difference in maximum standing diastolic blood pressure of -6 mmgHg and -4 mmHg when dosed with 10 and 20 mg tadalafil, respectively. Decreases in blood pressure were considered to be of clinical significance following a change from baseline (pre- tadalafil or placebo dose) of >30 mmHg for systolic blood pressure and >20 mmHg for diastolic blood pressure. The following table presents the number of subjects with clinically significant decreases in blood pressure that occurred in the 24 hours post-tadalafil or placebo dose. It shows that a similar number of subjects experienced clinically significant decreases in systolic and diastolic blood pressure following administration of 10 and 20 mg tadalafil and placebo. No subject had a clinically significant value of systolic blood pressure (<85 mmHg) or diastolic blood pressure (<45 mmHg).

Blood pressure parameter	Number of subjects with clinically significant decreases for the parameter		
	10 mg IC351 & 0.4 mg tamsulosin (N=18)	20 mg IC351 & 0.4 mg tamsulosin (N=18)	Placebo & 0.4 mg tamsulosin (N=18)
Supine systolic	1	1	2
Standing systolic	2	2	1
Supine diastolic	1	2	0
Standing diastolic	3	0	1
Total subjects	**5**	**4**	**4**

Number of Subjects with Clinically Significant Decreases in Blood Pressure Occurring in the Period 24 hours Post- Tadalafil or Placebo Dosing With Tamsulosin.

The following table shows the breakdown of adverse events by severity for each study arm. The overall incidence of drug-related adverse events was very low for all treatments. Four drug-related adverse events were reported during the study; one subject who received 10 mg IC351 and three subjects who received 20 mg tadalafil each experienced single episodes of myalgia. There were no severe or serious adverse events reported during the study.

Treatment	Subjects [%] with adverse events (all causalities)	Number of adverse events and severity (all causalities)	Subjects [%] with adverse events (drug-related[a])	Number of adverse events and severity (drug-related[a])
10 mg IC351 & 0.4 mg tamsulosin (N=18)	2 [11.1%]	Mild 1 Moderate 1 Severe 0 Total 2	1 [5.6%]	Mild 1 Moderate 0 Severe 0 Total 1
20 mg IC351 & 0.4 mg tamsulosin (N=18)	6 [33.3%]	Mild 1 Moderate 5 Severe 0 Total 6	3 [16.7%]	Mild 1 Moderate 2 Severe 0 Total 3
Placebo & 0.4 mg tamsulosin (N=18)	0 [0.0%]	Mild 0 Moderate 0 Severe 0 Total 0	0 [0.0%]	Mild 0 Moderate 0 Severe 0 Total 0

Summary of Treatment-Emergent Adverse Events During the Tamsulosin Interaction Study.

Tadalafil may be dosed to subjects receiving tamsulosin.

4. What is the effect of tadalafil on QT interval?

To address this concern, the sponsor tested the effect of a single 100 mg dose of tadalafil on QT interval in a positive- (intravenous ibutilide) and placebo- controlled trial. The positive control (ibutilide) at a dose of 0.0025 mg/kg was infused for 10 minutes—a level

the sponsor claims causes a 10 millisecond increase in QT interval. Although a 100 mg tadalafil dose is 5 times the highest to-be-marketed dose (20 mg), it does not yield 5 times the level of 20 mg dose exposure. At dose levels greater than 40 mg, tadalafil exposure increases less than proportionally with dose, likely due to decreased absorption.

The mean tadalafil Cmax and the mean Total IC710 (metabolite) Cmax in this study cover the respective Cmax values expected in the following situations:
(a) 20 mg tadalafil dosed to steady state
(b) 20 mg tadalafil coadministered with a 400 mg ketoconazole QD regimen
(c) 20 mg tadalafil coadministered with a 200 mg ritonavir BID regimen
(d) 20 mg tadalafil dosed to subjects with end-stage renal failure receiving hemodialysis
(e) 10 mg tadalafil dosed to subjects with mild or moderate renal impairment

The mean tadalafil $AUC_{0\rightarrow\infty}$ in this study likely covers the following situations:
1. the mean tadalafil AUC expected for a 20 mg dose at steady state
2. the mean tadalafil AUC expected when 20 mg tadalafil is dosed to subjects with end stage renal failure receiving hemodialysis
3. the mean tadalafil AUC expected when 10 mg tadalafil dosed to subjects with mild or moderate renal impairment

The mean tadalafil $AUC_{0\rightarrow\infty}$ in this study likely does not cover:
1. the mean tadalafil AUC expected when 20 mg tadalafil is coadministered with a 400 mg ketoconazole QD regimen
2. the mean tadalafil AUC expected when 20 mg tadalafil is coadministered with a 200 mg ritonavir BID regimen

The following table summarizes the effect of tadalafil, placebo, and the positive control (ibutilide) on corrected QT interval. Tadalafil caused a mean increase of 0.6 beats per minute in heart rate relative to baseline, while placebo caused a 2.5 beat per minute *decrease* in heart rate relative to baseline. The overall effect was a 3.1 increase in heart rate for tadalafil relative to placebo. The sponsor used several methods to correct QT interval for heart rate. For an ANOVA model fitting RR as a covariate, mean changes in "QTc" interval for tadalafil versus placebo was 3.3 msec with the two-sided 90% CI of (1.7, 5.0). The difference in the mean change from baseline for tadalafil relative to placebo with respect to an individual correction method ("QTcI"), the Fridericia correction ("QTcF"), and the in-house "Lilly" correction ("QTcL") was 2.8, 3.5 and 5.0 msec, respectively. The sponsor reported that QTcI and QTcF intervals were independent of heart rate while QTcL yielded a positive correlation with heart rate.

Comparison	Heart rate (bpm)	QT (ms)	QTc Model based (ms)	QTcI (Individual) (ms)	QTcF (Fridericia) (ms)	QTcL (Lilly) (ms)
100mg IC351	3.1	-2.4	3.3	2.8	3.5	5.0
(relative to placebo)	(1.7,4.5)	(-5.5,0.7)	(1.7,5.0)	(1.2,4.4)	(1.9, 5.1)	(3.3,6.7)
Ibutilide	1.8	5.7	9.6	8.9	9.5	10.4
(relative to placebo)	(0.4,3.2)	(2.0,9.4)	(7.6,11.6)	(6.9,10.8)	(7.6,11.4)	(8.5,12.4)
	-2.3	10.9	6.8	6.9	7.1	6.1
Ibutilide vs IC351	(-3.8,-0.8)	(7.2,14.7)	(5.0,8.7)	(5.0,8.8)	(5.3, 8.9)	(4.3,7.8)

* T_{max} for 100 mg IC351 and matched placebo, post-infusion (11 to 20 minutes) for Ibutilide

Summary of Effect of Tadalafil, Placebo, and the Positive Control (Ibutilide) on Response.

The following two tables summarize the results of the sponsor's outlier analysis. Note that it is difficult to compare the incidence of outlying values for ibutilide relative to tadalafil given that there were fewer measures taken when subjects received ibutilide than tadalafil. Based on an analysis of a total of 8,011 individual ECG QTc measurements, in the tadalafil (IC351) period, 0.7% and 0.9% of the measurements of change in QTcI and QTcF, respectively, from baseline were greater than 30 msec. These outlying values were observed in 8.6% and 15.1% of subjects. The effect of tadalafil on QT interval was greater than that for placebo but less than that for ibutilide—2% and 2.6% of the measurements of change in QTcI and QTcF, respectively, from baseline were greater than 30 msec in the ibutilide period. These outlying values were observed in 13.4% and 16.4% of subjects. In the placebo period, 0.2% and 0.3% of the measurements of change in QTcI and QTcF, respectively, from baseline were greater than 30 msec and these outlying values were observed in 6.6% and 7.7% of subjects.

No subject experienced a QTc change from baseline in the placebo, tadalafil and ibutilide periods greater than 60 msec. Approximately ten percent (10%) of the outlying values were >45 msec. No individual post-baseline QTc value exceeded 450 msec in the tadalafil and placebo periods.

	100 mg IC351 N=3713 n(%)	Placebo N=3636 n(%)	Ibutilide N=665 n(%)
Change QTcI interval >30 ms	25(0.7)	8(0.2)	13(2.0)
Change QTcF interval >30 ms	33(0.9)	10(0.3)	17(2.6)
Change QTcL interval >30 ms	67(1.8)	14(0.4)	22(3.3)

Summary of Outlier Changes in QTcI, QTcF, and QTcL Values. Number and percent of observations with a change from baseline >30 msec.

	100 mg IC351 N=93 n(%)	Placebo N=91 n(%)	Ibutilide N=67 n(%)
Change QTcI interval >30 ms	8(8.6)	6(6.6)	9(13.4)
Change QTcF interval >30 ms	14(15.1)	7(7.7)	11(16.4)
Change QTcL interval >30 ms	22(23.7)	10(11.0)	14(20.9)

Number (Percent) of Subjects with at Least One Change in QTcI, QTcF or QTcL >30 msec.

The purpose of the positive control in this study was to demonstrate that the study is sensitive enough to detect a change in QTc interval on the order of 10 msec. Had the sponsor's test compound (tadalafil) caused a change in QT interval to a clinically significant extent, the response to the positive control would be of little concern. The sponsor's claim that tadalafil causes no significant change in QT interval, however, necessitates evaluation of the performance of the positive control.

Therapeutic doses of ibutilide are associated with large changes in QT interval, so the sponsor used a low dose of ibutilide. There is little published information on the dose/concentration–response relationship for low dose ibutilide. The sponsor ran a dose-finding study for intravenous ibutilide and claims to have data showing that 0.0025 mg/kg ibutilide infused for 10 minutes causes a QTcB change of 9.0 msec (min: [redacted] msec, max: [redacted]; N=8). The dose-finding study enrolled 16 healthy males, 18 to 65 years of age.

An extensive literature search revealed only one published study with a dose approximating that used by the sponsor.[1] In that report, a 0.003 mg/kg intravenous dose of ibutilide infused for 10 minutes to 38 males aged 21-40 years was associated with an average change of 30 msec (SEM=2.39) in QTcB interval.[1,2]

What is the reason for the discrepancy between the response to intravenously infused ibutilide at nearly identical doses (sponsor: 0.0025 mg/kg; published report: 0.003 mg/kg)?

One possible explanation is the difference in the age between the subjects of the two studies. Another possible explanation is that ibutilide has a very sharp dose-response curve right between the 0.0025 mg/kg and the 0.003 mg/kg dose. That is, 0.0025 mg/kg causes a 10 msec change but 0.003 mg/kg causes a 30 msec change. There are no data available to evaluate this possibility.

A potential concern is that the 0.0025 mg/kg dose causes a 30 msec change in QTc but the study design was such that a drug which causes a 30 msec in QTc appeared to cause a 10 msec change. One consequence would be that tadalafil—which appears to prolong QTc by approximately 5 msec—actually causes a greater level of prolongation.

The source of the discrepancy was a difference in dose between the information in the literature and the sponsor's protocol. For reasons of safety, the sponsor's protocol required that the infusion be stopped if two consecutive readings of QTcB>12 msec were observed or a single reading of QTcB >30 msec was observed in a subject. The following two tables show the results of the sponsor's dose-finding study for ibutilide.

	Maximum increase in QTc interval (ms)					
	Placebo	0.0009 mg/kg ibutilide	0.001 mg/kg ibutilide	0.015 mg/kg ibutilide	0.002 mg/kg ibutilide	0.0025 mg/kg ibutilide
	14 [1/3]	11 [2/1]	18 [1/3]	19 [1/5]	27 [1/3]	18 [1/7]
	12 [1/4]	9 [2/2]	13 [1/4]	7 [1/6]	19 [1/4]	25 [1/8]
	8 [1/5]	9 [2/3]	20 [2/1]	52 [2/1]	24 [1/5]	21 [2/4]
	5 [1/6]	29 [3/1]	33 [2/2]	23 [2/2]	13 [1/6]	15 [2/4]
	7 [1/7]	14 [3/2]	18 [2/3]	16 [2/3]	14 [1/7]	18 [2/5]
	8 [1/8]		40 [2/6]	43 [2/9]	48 [1/8]	14 [2/5]
	8 [2/4]		16 [3/1]	16 [3/1]	60 [2/7]	95 [2/6]
	8 [2/5]		13 [3/2]		18 [2/8]	22 [2/8]
	62 [2/6]				70 [2/9]	
	44 [2/7]					
	29 [2/7]					
	4 [2/8]					
	22 [2/9]					
Mean	17.8	14.4	21.4	25.1	32.6	28.5
Mean change[a]	17.8[b]	-3.4	3.6	7.3	14.8	10.7
Median	8	11	18	19	24	19.5
Min						
Max						
N	13	5	8	7	9	8

Source: Listing 5

[Centre/Subject number]

[a] Mean change from placebo mean

[b] Absolute value

Summary of Maximum Increases in QTc Interval (ms) During the 1 Hour Period Following Ibutilide Infusion.

	Average change in QTc interval (ms)					
	Placebo	0.0009 mg/kg ibutilide	0.001 mg/kg ibutilide	0.015 mg/kg ibutilide	0.002 mg/kg ibutilide	0.0025 mg/kg ibutilide
	-0.07 [1/3]	0.68 [2/1]	5.21 [1/3]	3.45 [1/5]	9.07 [1/3]	6.61 [1/7]
	0.80 [1/4]	-1.14 [2/2]	2.48 [1/4]	0.93 [1/6]	9.22 [1/4]	8.38 [1/8]
	3.13 [1/5]	0.50 [2/3]	1.23 [2/1]	9.19 [2/1]	8.13 [1/5]	8.68 [2/4]
	-4.07 [1/6]	-1.83 [3/1]	6.73 [2/2]	7.23 [2/2]	4.13 [1/6]	7.85 [2/4]
	1.10 [1/7]	4.48 [3/2]	9.15 [2/3]	7.11 [2/3]	4.94 [1/7]	4.56 [2/5]
	-10.4 [1/8]		3.16 [2/6]	11.66 [2/9]	9.49 [1/8]	8.27 [2/5]
	-0.82 [2/4]		2.66 [3/1]	-0.50 [3/1]	14.14 [2/7]	21.00 [2/6]
	-4.60 [2/5]		5.21 [3/2]		6.88 [2/8]	1.39 [2/8]
	7.54 [2/6]				9.50 [2/9]	
	1.97 [2/7]					
	-2.17 [2/7]					
	-5.30 [2/8]					
	-0.77 [2/9]					
Mean	-1.068	0.818	4.548	7.038	8.631	8.959
Median	-0.77	0.50	4.19	7.11	9.07	8.06
Min						
Max						
N	13	5	8	7	9	8

Source: Listing 5

[Centre/Subject number]

Mean Change in QTc Interval (msec) During the 1 Hour Period Following Ibutilide Infusion.

The extent to which there is a direct exposure-response relationship for ibutilide validates the sponsor's dosing scheme for ibutilide. Note that the maximum change in QTcB observed occurred 5 minutes after the termination of infusion (at 15 minutes) in the published study—very much a direct effect relation.

Given that the study was well-powered for a comparison with placebo (N=90 subjects) and given the tight confidence intervals on the response to placebo, ibutilide, and tadalafil, the results of the study are trustworthy. As such, tadalafil appears to have a small, but clinically insignificant effect on QT interval.

The sponsor submitted a plot and regression line fit to the data for the change in QTcI from baseline as a function of tadalafil plasma concentration at 3, 4, 6, and 24 hours postdose. The sponsor reported that a fit to the pooled dataset suggests that there is a flat slope (<0.002 ms per ng/mL, p>0.10) over the entire range of concentration values and claims that this suggests that there is no concentration-related increase in QTc for tadalafil. There are numerous difficulties with this claim. First, given that there were few data points at high concentrations, each of these extreme points likely exert great leverage. Second, the sponsor offered no comment regarding the goodness of fit of the model. There was no plot summarizing how well the population fit agreed with models for individual datasets. Finally, response was smaller with respect to QTcI than any other correction method used, thus, this metric likely provides the smallest estimate of effect. Regardless, the dose-response information support the claim of little significant effect on QT interval.

The following table shows the results with respect to adverse events. Eighty eight percent (88%) of subjects receiving 100 mg tadalafil experienced a total of 290 drug-related adverse events. In contrast, 15% and 1% of subjects receiving placebo and ibutilide experienced 41 and 14 drug-related adverse events, respectively. Three (3) of the adverse events on tadalafil were severe, while zero of the adverse events on placebo or ibutilide were of a severe nature. Sixty six (66) of the adverse events on tadalafil were moderate, while 12 and 4 of the adverse events on placebo and ibutilide, respectively, were of a moderate nature. Back pain was reported by 22.8% (21/92) subjects receiving 100 mg tadalafil in contrast with 2.2% and 1.5% of subjects receiving placebo and ibutilide, respectively. Myalgia was reported by 19.6% (18/92) of subjects receiving 100 mg tadalafil in contrast with 1% and 0% of subjects receiving placebo and ibutilide, respectively. Dizziness was reported by 10.9% of subjects receiving 100 mg tadalafil in contrast with 2.2% and 0% of subjects receiving placebo and ibutilide, respectively.

Treatment	Subjects [%] with adverse events (all causalities)	Number of adverse events and severity (all causalities)		Subjects [%] with adverse events (drug-related*)	Number of adverse events and severity (drug-related*)	
100 mg IC351 (N=92)	84 [91.3%]	Mild	240	81 [88.0%]	Mild	219
		Moderate	68		Moderate	66
		Severe	4		Severe	3
		Not known	2		Not known	2
		Total	314		Total	290
Placebo (N=91)	26 [28.6%]	Mild	42	15 [16.5%]	Mild	29
		Moderate	16		Moderate	12
		Severe	0		Severe	0
		Not known	0		Not known	0
		Total	58		Total	41
0.002 mg/kg ibutilide (N=67)	25 [37.3%]	Mild	38	1 [1.5%]	Mild	10
		Moderate	7		Moderate	4
		Severe	0		Severe	0
		Not known	1		Not known	0
		Total	46		Total	14

Frequency of Treatment-Emergent Adverse Events by Severity for Study LVFB.

Given the small mean effect of tadalafil on QTc and the few outlying values, the drug appears not to cause a clinically significant change in QTc interval. The effect of tadalafil on QTc should be reported in the Clinical Pharmacology section of the label.

The high incidences of back pain and myalgia in subjects receiving high doses of tadalafil may be noted in the labeling.

References

1. Rodriguez I, Kilborn MJ, Liu XK, Pezzullo JC, Woosley RL. Drug-induced QT prolongation in women during the menstrual cycle. JAMA. 2001 Mar 14;285(10):1322-6.
2. Personal communication and exchange of data with RL Woosley (co-author of publication listed above).

5. What are the absorption characteristics of tadalafil?

To address this question, the tmax data on all studies submitted in the original application were reviewed. (See below.) The median tmax of tadalafil is 2 hours.

1. Study LVBX: Bioequivalence and Dose proportionality study in healthy subjects

5 mg	median tmax: 2 hours; range: 1,6 hours	N=15
10 mg	median tmax: 2 hours; range: .5,4 hours	N=15
20 mg	median tmax: 3 hours; range: 1,4 hours	N=15
Another group:		
10 mg	median tmax: 2 hours; range: 1,6 hours	N=24

2. Study LVAU: Single and multiple dose PK

5 mg at steady state:	median tmax: 3 hours; range: 1,8 hours	N=12
10 mg at steady state:	median tmax: 3 hours; range: 1,4 hours	N=12

3. Study LVBH: PK in elderly

10 mg	median tmax: 3.3 hours; range: 2,4 hours	N=6

4. Study LVBW: Single dose PK in elderly vs. young

10 mg elderly	median tmax: 2 hours; range: 1,4 hours	N=12
10 mg young	median tmax: 2.5 hours; range: 1,6 hours	N=12

5. Male — PK comparison

10 mg to males: single dose	median tmax: 3.5 hours; range: 1,8 hours	N=12
10 mg to males: steady state	median tmax: 3 hours; range: 1,4 hours	N=12

6. Study LVAS: PK in diabetics and healthy subjects

10 mg to healthy	median tmax: 2 hours; range: 1,8 hours	N=12

7. Study LVAZ: PK w/ Ketoconazole 200 mg or rifampicin

10 mg alone	median tmax: 2 hours; range: 1,6 hours	N=12
10 mg alone	median tmax: 2 hours; range: 0.5,4 hours	N=12

6. How do the dissolution conditions and specifications assure in vivo performance?
Pivotal trials were conducted using tadalafil tablets manufactured in Indianapolis. The to-be-marketed tablets will be manufactured in Carolina, Puerto Rico. In this resubmission, dissolution data from Indianapolis and Puerto Rico were submitted and reviewed on 5 mg, 10 mg, and 20 mg strength tablets.

In this submission and the original submission, the sponsor provided multi-point dissolution specifications for tadalafil. The sponsor's justification was that: (1) assurance of ——— is important for efficacy and (2) complete release of Cialis is essentially achieved at 30 minutes in the application medium, thus, a multi-point dissolution profile at the specification timepoints, 10 and 30 minutes was proposed by the sponsor.

Given that this is an ——— formulation, a single time point is adequate to specify dissolution. The drug is — dissolved at — minutes in a media that includes surfactant (SDS).

The following dissolution conditions were used.

Strength: 5 mg, 10 mg, 20 mg
Apparatus Type: ———

Volume:
Speed of Rotation:
Brief Description of Dissolution Analytical Method:

The following tables provide a summary of computations performed on the individual data to evaluate dissolution conditions.

5 mg dose

Time (min)	Mean (sd) of Minimum Dissolution		Mean (sd) of Average Dissolution	
	Indianapolis	Puerto Rico	Indianapolis	Puerto Rico
10	69.8 (4.1)	70.3 (12.1)	80.1 (2.4)	81.9 (3.9)
20	88.6 (1.7)	89.6 (5.6)	93.8 (1.3)	94.3 (1.7)
30	92.6 (1.4)	93.9 (2.1)	96.3 (1.0)	96.9 (sd: 1.1)

10 mg dose

Time (min)	Mean (sd) of Minimum Dissolution		Mean (sd) of Average Dissolution	
	Indianapolis	Puerto Rico	Indianapolis	Puerto Rico
10	68.7 (2.9)	68 (5.5)	78.9 (1.9)	78.1 (3.1)
20	89 (2.2)	89.1 (3.3)	93.9 (1.1)	93.3 (1.3)
30	94.0 (1.6)	94.2 (1.9)	97.4 (0.5)	96.8 (1.2)

20 mg dose

Time (min)	Mean (sd) of Minimum Dissolution		Mean (sd) of Average Dissolution	
	Indianapolis	Puerto Rico	Indianapolis	Puerto Rico
10	58.4 (4)	65 (7.7)	71.8 (3)	75.1 (1.9)
20	84.2 (1.5)	87.9 (2.6)	90 (0.9)	91.4 (1.4)
30	91.0 (1.2)	93.6 (1.5)	94.7 (0.71)	95.6 (0.9)

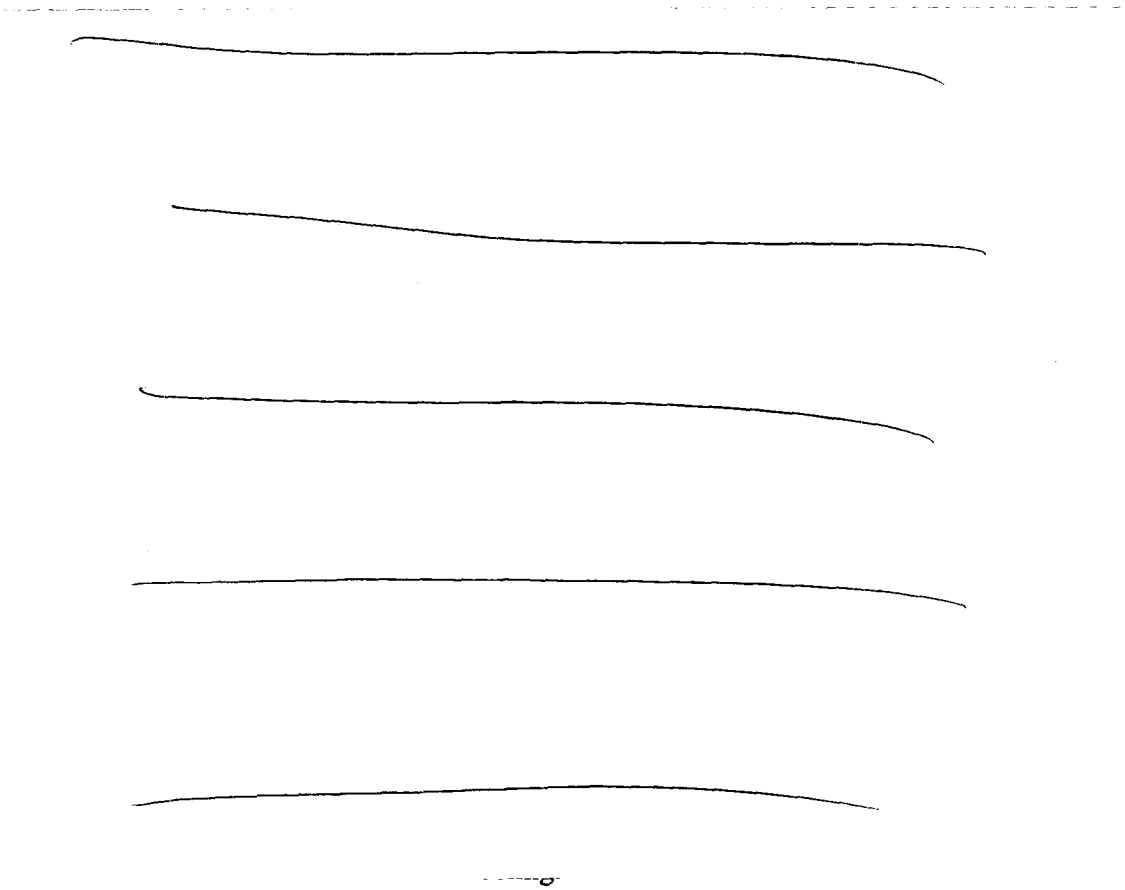
Based on the above tables and discussion with the DPE II management, the recommended dissolution specification is: % dissolved (Q=) in 30 minutes.

The following tables of f2 values computed on data from 5 mg, 10 mg and 20 mg doses indicate that the profiles are similar . The values were verified by independent calculations. Thus, 5 mg, 10 mg, and 20 mg tablets manufactured in Carolina, Puerto Rico are comparable to those manufactured in Indianapolis.

__1__ page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

(b4)

V. Detailed Labeling Recommendations



VI. Appendices

A. Proposed Package Insert (Submitted separately to DFS)

B. Individual Study Reviews
Appended to this file.

C. Consult Review
None requested.

D. Cover Sheet and OCPB Filing/Review Form
Refer to earlier submission to DFS.

Individual Study Reviews (6 Studies)
1. H6D-EW-LVDT:
A Study to Investigate the Tolerability and Pharmacokinetics of IC351 in Subjects on Hemodialysis for Renal Failure

Summary/Conclusions
• The sponsor reported the change in exposure with respect to all dose groups considered together. In this case, there was a 2.1-fold increase in tadalafil AUC and a 1.4-fold increase in tadalafil Cmax for ESRF subjects relative to healthy subjects.

That breaks down by dose group as follows:
*5 mg dose tadalafil in ESRF relative to healthy subjects:
No change in AUC tadalafil
22% decrease in Cmax tadalafil
*10 mg dose tadalafil in ESRF relative to healthy subjects:
1.1-fold – 4.8-fold increase in AUC tadalafil
0-2.2-fold increase in Cmax tadalafil
*20 mg dose tadalafil in ESRF relative to healthy subjects:
2.7-fold increase in AUC tadalafil
2-fold increase in Cmax tadalafil

• For all dose groups considered together, there was a 3.2-fold increase in Total IC710 AUC and a 1.6-fold increase in Total IC710 Cmax for ESRF subjects relative to healthy subjects.
That breaks down by dose group as follows:
*5 mg dose tadalafil in ESRF relative to healthy subjects
2.7-fold increase in AUC
1.6-fold increase in Cmax
*10 mg dose tadalafil in ESRF relative to healthy subjects:
2.1-3.3-fold increase in AUC IC710
1.3-1.8-fold increase in Cmax IC710

• The increased tadalafil exposure in ESRF subjects compared to healthy subjects cannot be explained by a difference in the distribution pharmacokinetics for tadalafil:
+Mean protein binding of tadalafil in ESRF subjects undergoing hemodialysis is approximately 96%—similar to that observed in healthy subjects (94%).
+Protein binding did not appear to be different between pre- and postdose, or between the 10 and 20 mg dose groups.

•Hemodialysis contributes negligibly to elimination of either IC351 or its methylcatechol glucoronide. (Post-dialysis values of parent are 90% of pre-dialysis values and metabolite values are 1.2-fold greater post-dialysis.)

• Cmax, AUC, t½, and Tmax parameters for subjects with ESRF were different than for healthy subjects and for subjects with mild and moderate renal impairment receiving the same dose:

For the 10 mg dose
*Median tadalafil Tmax in ESRF (2-4 hours) was greater than that in mild renal failure (2 hours) and moderate renal failure (2 hours) and in healthy subjects (1 hour).
*Median tadalafil t½ in ESRF (15.2-24.8 hours) was between that in mild and moderate renal failure (26 hours and 22 hours, respectively) and healthy subjects (14 hours).
*Median Total IC710 tmax in ESRF (52.4-77.5 hours) was greater than that in mild (36 hours) and moderate (48 hours) renal failure and in healthy subjects (18 hours).

For the 5 mg dose
*Median tadalafil Tmax in ESRF (3 hours) was greater than that in mild renal failure (2 hours) and moderate renal failure (0.5 hours) and in healthy subjects (1 hour).
*Median tadalafil t½ in ESRF (13.8 hours) was less than that in mild and moderate renal failure (25 hours and 26 hours, respectively) and healthy subjects (18 hours).
*Median Total IC710 t½ in ESRF (51.6 hours) was greater than that in mild (31 hours) and moderate (51 hours) renal failure and in healthy subjects (20 hours).
*Median Total IC710 tmax in ESRF (55.3 hours) was greater than that in mild (24 hours) and moderate (42 hours) renal failure and in healthy subjects (20 hours).

• There was a discrepancy in all tadalafil parameters between the two study sites for 10 mg dose. The site (Polish) with the lower values of exposure had more women.

• There is a greater than dose proportional increase in AUC and Cmax for an increase in dose from 5 mg to 20 mg. That is, there is an 11.1-fold increase in AUC and a 7.9-fold increase in Cmax for a 4-fold increase in dose.

• There is a greater than dose proportional increase in Tadalafil's AUC and Cmax for the UK cohort with an increase in dose from 5 mg to 10 mg. That is, there is an 8.4-fold increase in AUC and a 5-fold increase in Cmax for a 2-fold increase in dose.

• 1/6 subjects (16.7%) receiving 20 mg tadalafil experienced diziness. No subject experienced a severe adverse event.

Background

• A previous study (LVAJ) compared the pharmacokinetics, safety and tolerability of a single dose of 5 or 10 mg tadalafil in subjects with mild or moderate renal impairment (who were not undergoing hemodialysis) to healthy subjects.

• LVAJ demonstrated that exposure to tadalafil and its primary metabolites, Total IC710, was significantly higher following administration of tadalafil to the renally impaired subjects

• The 10 mg dose was poorly tolerated by subjects in LVAJ with mild renal impairment.

Objective

• To investigate the pharmacokinetics of 5 mg, 10 mg, and 20 mg tadalafil and the total hydrolyzed methylcatechol glucuronide metabolite (Total IC710) in subjects on hemodialysis.

• To assess the safety and tolerability of a single 5 mg, 10 mg, and 20 mg oral dose of tadalafil in subjects with renal impairment on hemodialysis.

Design

• Open-label, sequential dosing, 2-center study

• Male or female subjects, 25-75 years, with ESRF who were receiving three hemodialysis sessions per week

• 16 subjects, 24 dosing occasions (some subjects escalated one level higher):

5 mg	N=8
10 mg	N=16
20 mg	N=8

• Single doses of 5, 10 or 20 mg tadalafil administered approximately 24 to 30 hours prior to their first hemodialysis session in the study period

• Sampling for protein binding assessment predose and 4 hours postdose

Sponsor's Planned Analyses

• Non-compartmental assessment of the tadalafil and Total IC710 plasma concentration versus time data

• Cmax and tmax were determined from the observed plasma concentration versus time profiles.

• Statistical Methodology: the arithmetic mean, arithmetic standard deviation (SD), arithmetic coefficient of variation (CV%), geometric mean, geometric CV%, median, minimum value (min), maximum value (max) and the number of observations (N) was determined. Pharmacokinetic data from the present study and studies LVAJ (healthy subjects only) and LVBX Part B (tadalafil only) were combined for the analysis. A statistical comparison of the parameters AUC and Cmax for both tadalafil and Total IC710 was performed to compare the hemodialysis subjects with the healthy subjects.

Results

Figure 1 presents the arithmetic mean plasma-concentration-time profiles for tadalafil and Total IC710 following 5, 10 and 20 mg single oral doses administered to ESRF subjects undergoing hemodialysis. Table 1 and Table 3 present the summary statistics for select pharmacokinetic parameters of IC351 and Total IC710, respectively, with separate summary statistics for the two sites testing the 10 mg dose level. Table 2 and Table 4 show the ratio of tadalafil and Total IC710 parameters for the 10 mg and 20 mg tadalafil doses relative to the 5 mg value, respectively.

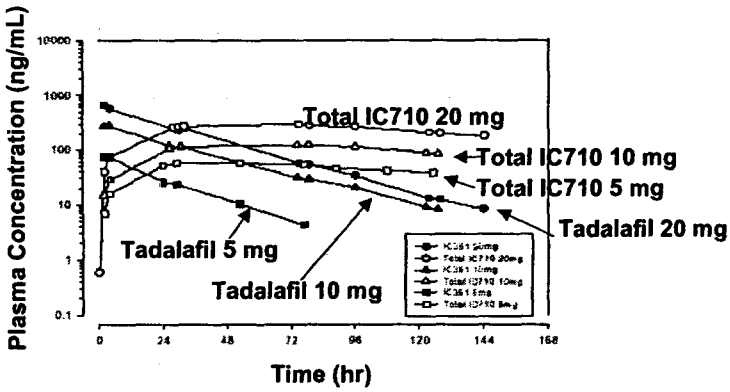


Figure 1. Arithmetic Mean Plasma Concentrations of Tadalafil and Total IC710 versus Time Following Single Oral Administration of 5, 10 and 20 mg Tadalafil to End-Stage Renal Failure Subjects Undergoing Hemodialysis.

Parameter	5 mg IC351 (N=6)	10 mg IC351		20 mg IC351 (N=6)
		Polish cohort (N=6)	UK cohort (N=6)	
AUC (µg*h/L)	1633 (63.0)	4023 (38.2)	13749 (36.7)	18090 (38.8)
AUC(0-t_n) (µg*h/L)	1587 (61.7)	3983 (37.3)	13333 (34.8)	17878 (37.6)
C_{max} (µg/L)	78.6 (21.6)	186 (17.2)	394 (20.8)	621 (26.6)
t_{max} (h)[a]	3.00	4.00	2.04	2.04
$t_{½}$ (h)	13.8 (51.3)	15.2 (41.6)	24.8 (37.9)	18.7 (34.6)
CL/F (L/h)	3.06 (63.0)	2.49 (38.2)	0.73 (36.7)	1.11 (38.8)
V_z/F (L)	60.9 (18.2)	55.0 (19.9)	26.1 (22.9)	29.8 (16.9)

Source: Section 14.2.2 (Table 2)
µg/L is equivalent to ng/ml.
N = number of subjects
NC = not calculated
[a]Median (min-max) data

Table 1. Geometric Mean (CV%) Pharmacokinetic Parameters for Tadalafil (IC351) Following Single Dose Administration of 5, 10 and 20 mg Tadalafil to End-Stage Renal Failure Subjects.

• Ratio of tadafil PK parameters in Table 1 relative to 5 mg dose:

	10 mg Tadalafil		20 mg Tadalafil
	Polish Cohort (N=6)	UK Cohort (N=6)	(N=6)
AUC	2.5	8.4	11.1
Cmax	2.4	5.0	7.9
Tmax	1.3	0.67	0.67
t½	1.1	1.8	1.4
CL/F	0.81	0.24	0.36

Vz/F	0.90	0.43	0.49

Table 2. Ratio of Tadalafil Pharmacokinetic Parameters in Table 1 Relative to the 5 mg Dose.

Note in Table 1:
• Large variability in tadalafil's AUC and CL/F for 5 mg dose group.
• Discrepancy in all tadalafil parameters between the two study sites for 10 mg dose.

Note in Table 2:
• There is a greater than dose proportional increase in Tadalafil's AUC and Cmax for the UK cohort with an increase in dose from 5 mg to 10 mg. That is, there is an 8.4-fold increase in AUC and a 5-fold increase in Cmax for a 2-fold increase in dose.
• There is a greater than dose proportional increase in AUC and Cmax for an increase in dose from 5 mg to 20 mg. That is, there is an 11.1-fold increase in AUC and a 7.9-fold increase in Cmax for a 4-fold increase in dose.

		10 mg IC351		
Parameter	5 mg IC351 (N=6)	Polish cohort (N=6)	UK cohort (N=6)	20 mg IC351 (N=6)
AUC (µg*h/L)	6051 (34.0)[a]	16837 (17.8)[b]	NC	NC
AUC(0-t_n) (µg*h/L)	5392 (38.7)	9983 (28.5)[c]	15891 (34.8)	32229 (24.5)
C_{max} (µg/L)	64.2 (33.4)	109 (35.6)	158 (33.5)	300 (26.1)
t_{max} (h)[c]	55.3	52.4	77.5	74.1
$t_{½}$ (h)	51.6 (52.2)[c]	66.2 (40.7)[c]	NC	NC
CL/F (L/h)	NC	NC	NC	NC
V_z/F (L)	NC	NC	NC	NC
MR	3.40 (69.5)	2.51 (65.2)	1.19 (70.2)	1.80 (53.9)

Source: Section 14.2.2 (Table 2)
µg/L is equivalent to ng/mL.
N = number of subjects
MR = metabolic ratio (AUC(0-t_n)m/AUC(0-t_n))
NC = not calculated
[a] N=3
[b] N=4
[c] Median (min-max) data

Table 3. Geometric Mean (CV%) Pharmacokinetic Parameters of Total IC710 Following Single Dose Administration of 5, 10 and 20 mg Tadalafil to End-Stage Renal Failure Subjects.

• Ratio of Total IC710 PK parameters in Table 3 relative to 5 mg dose Tadalafil:

	10 mg Tadalafil		20 mg Tadalafil
	Polish Cohort (N=6)	UK Cohort (N=6)	(N=6)
AUC	2.8	NC	NC
Cmax	1.7	2.5	4.7
Tmax	0.95	1.4	1.3
t½	1.3	NC	NC
CL/F	NC	NC	NC
Vz/F	NC	NC	NC

MR	0.74	0.35	0.53

Table 4. Ratio of Total IC710 Pharmacokinetic Parameters Relative to the 5 mg Dose.

Note in Table 3:
• Discrepancy in parameters between the two study sites for 10 mg dose.
• Tmax increases with dose.

Note in Table 4:
• Changes in Cmax are approximately dose-proportional.
• Sponsor mentions that Total IC710 AUC could only be determined for 3 and 4 subjects at the 5 and 10 mg dose levels, respectively, due to the flat nature of the profiles. The geometric mean extrapolated area was 20.4%, therefore AUC values for Total IC710 at the 5 mg dose should be interpreted with caution.

Table 5 shows the ratio of pre- and post- hemodialysis concentrations of tadalafil and Total IC710 following 5, 10, and 20 mg tadalafil doses.

Analyte	Parameter	Ratio of post-/pre-haemodialysis (90% CI)
IC351	IC351 concentration (ng/mL)	0.91 (0.85 to 0.96)
Total IC710	Total IC710 concentration (ng/mL)	1.18 (1.11 to 1.25)

Table 5. Comparison of Pre- and Post-Hemodialysis Concentrations of Tadalafil (IC351) and Total IC710 following 5, 10 and 20 mg Tadalafil.

Note in Table 5:
The post-dialysis values of parent are 90% of pre-dialysis values and metabolite values are 1.2-fold greater post-dialysis.

Figure 2 shows the concentration-time data for individuals who received the 10 mg dose. Note that this dose yielded different results depending on the study site.

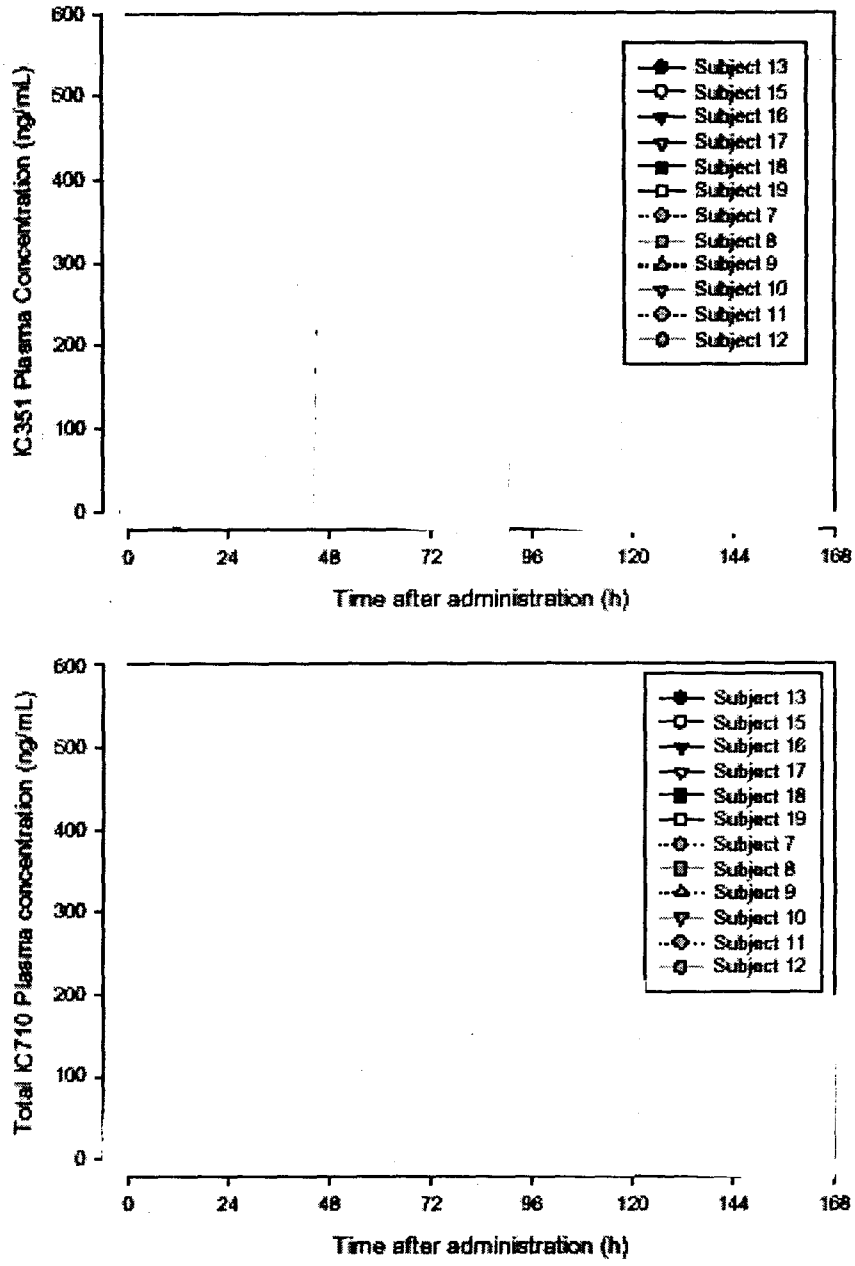


Figure 2. Plasma Concentrations of Tadalafil (Top Panel) and Total IC710 (Bottom Panel) versus Time Following Single Oral Administration of 10 mg Tadalafil (IC351) to End-Stage Renal Failure Subjects Undergoing Hemodialysis (Subjects 7 to 12 Polish Cohort, 13 to 19 UK Cohort).

Note in Figure 2:
Less discrepancy among metabolite profiles for the 2 study sites than for the parent profiles.

Figure 3 shows the discrepancy for the 10 mg dose group study sites in terms of Cmax and AUC.

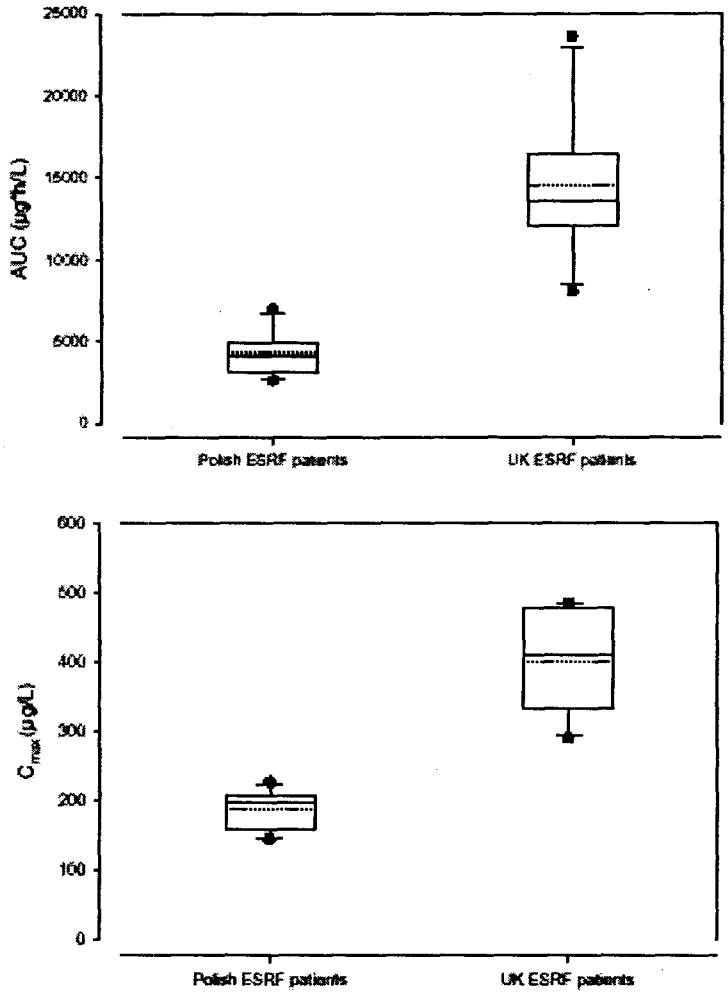


Figure 3. Box and Whisker Plots of Tadalafil AUC (upper panel) and Cmax (lower panel) Following Single Oral Dose Administration of 10 mg Tadalafil to Polish and UK End-Stage Renal Failure Subjects Undergoing Hemodialysis. - - - - mean value —— median value

The sponsor submitted a comparison of the pharmacokinetic data from subjects in the current study to data from previously reviewed studies (Study LVBX and Study LVAJ) in which 5, 10, and 20 mg tadalafil was administered to either healthy subjects or both healthy and renally impaired subjects. Figure 4 is a plot of the mean concentration–time data for the studies in healthy subjects with individual data from the presently reviewed study (LVDT).

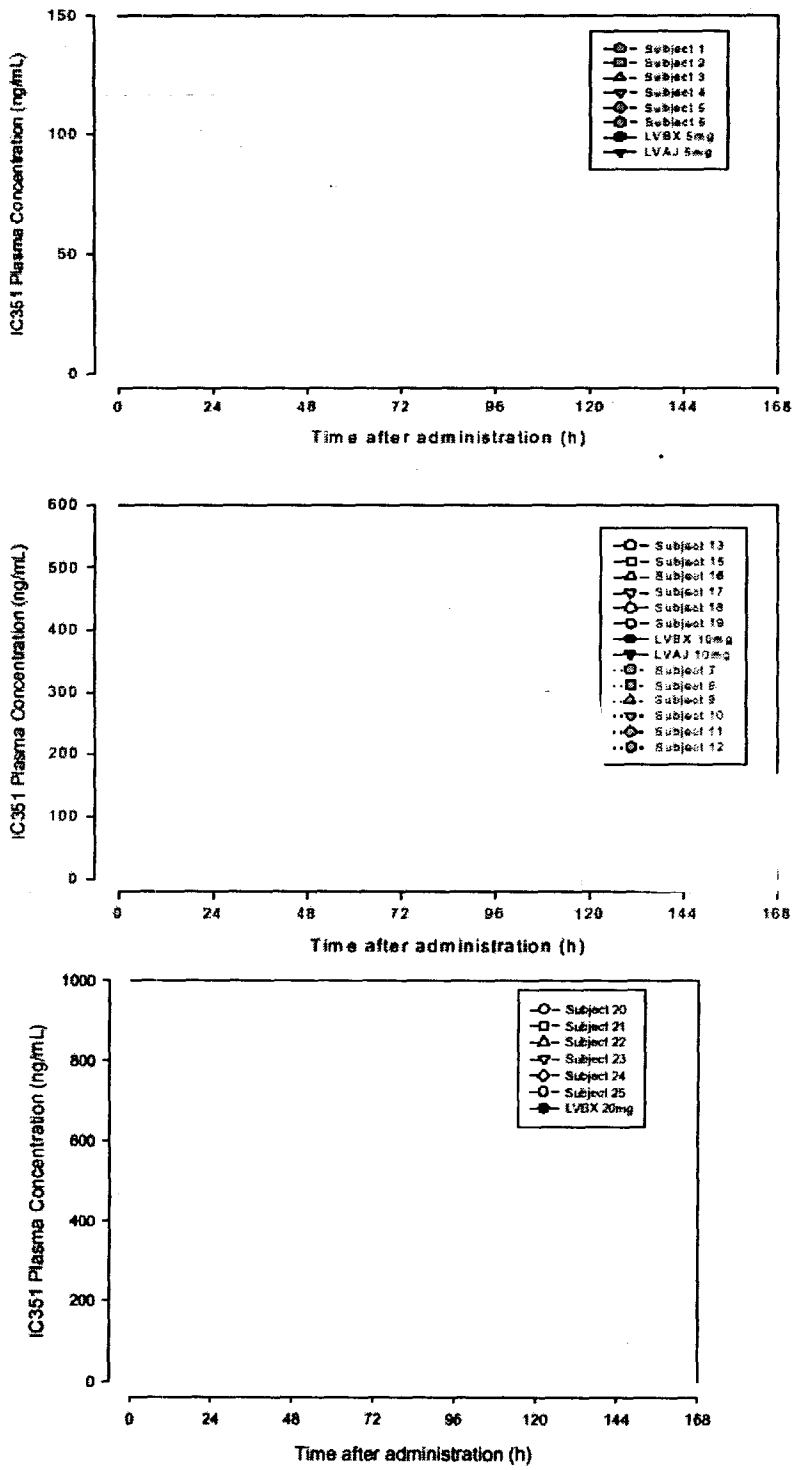


Figure 4. Plasma Concentrations of Tadalafil vs Time Following Single Oral Administration of Tadalafil to End-Stage Renal Failure Subjects Undergoing Hemodialysis (LVDT) and Healthy Subjects (LVBX and LVAJ) (Upper Panel, 5mg; Middle Panel, 10mg; Lower Panel, 20mg dose). Note that subjects 1-12 in Polish cohort and subjects 13 to 25 in UK cohort.

Note in Figure 4:
• Some ESRF subjects receiving 5 mg tadalafil have a similar profile as healthy subjects receiving 5 mg tadalafil. The individual profiles of subjects with ESRF do not distribute evenly around the mean for healthy subjects; the rest receiving the 5 mg dose exceed the mean values for Study LVBX and Study LVAJ.
• Some ESRF subjects in the Polish cohort receiving 10 mg tadalafil have a similar profile as healthy subjects receiving 10 mg tadalafil. The individual profiles of subjects with ESRF do not distribute evenly around the mean for healthy subjects; the rest receiving the 10 mg dose exceed the mean values for Study LVBX and Study LVAJ.
• No ESRF subjects receiving the 20 mg dose has a similar profile as the mean healthy subject receiving 20 mg tadalafil in Study LVBX.

The sponsor provided Table 6 to summarize a statistical comparison of the pharmacokinetic parameters of tadalafil and Total IC710 from the present study and from studies LVAJ and LVBX (healthy subjects only). Note that this table reports the statistics based on data pooled from all dose groups and then separately for each of the 10 mg dose groups.

Analyte	Comparison	Population	Parameter	Ratio (90% CI)
IC351	LVDT : LVAJ and LVBX (Healthy)	Overall	AUC (norm)	2.09 (1.70 to 2.56)
			C_{max} (norm)	1.41 (1.23 to 1.62)
		Poland	AUC (norm)	1.27 (0.94-1.73)
			C_{max} (norm)	0.91 (0.76-1.09)
		UK	AUC (norm)	3.29 (2.65-4.08)
			C_{max} (norm)	2.14 (1.86-2.47)
Total IC710	LVDT : LVAJ and LVBX (Healthy)	Overall	AUC (norm)	3.15 (2.25 to 4.41)
			AUC ($0\text{-}t_n$) (norm)	2.66 (2.11 to 3.35)
			C_{max} (norm)	1.55 (1.26 to 1.90)

Table 6. Statistical Comparison of IC351 (Tadalafil) and Total IC710 Pharmacokinetic Parameters Following Dosing with 5, 10 and 20 mg IC351 (Studies LVDT [the Present Study], LVAJ and LVBX).

Note in Table 6:
• When data from all dose groups are analyzed, average tadalafil AUC increases 2.1-fold and average tadalafil Cmax increases 1.4-fold, respectively, for subjects with End Stage Renal Failure relative to healthy subjects. At the 10 mg dose level, average Total IC710 AUC increases 3.2-fold and average Total IC710 Cmax increases 1.6-fold. All of these changes are statistically significant.

The results reported in Table 7- Table 13 below show the relative change in AUC and Cmax for each dose group separately, as opposed to Table 6 which pools the data from all dose groups. Note that the analysis of the results reported in Tables 7-13 (which follows in this review) shows that Table 6 represents the trend for IC710, but not necessarily for tadalafil.

Table 7 and Table 8 contain Tadalafil and IC710 pharmacokinetic parameters estimated from a study in which 10 mg tadalafil was dosed to healthy and renally impaired subjects.

	Group		
Parameter	Healthy subjects (N=8)	Mild renal impairment (N=5)	Moderate renal impairment (N=6)
AUC (µg*h/L)	2868 (44.2)	6280 (46.1)	4911 (50.1)
AUC(0-24) (µg*h/L)	2025 (32.6)	2899 (27.5)	2687 (23.9)
C_{max} (µg/L)	183 (31.2)	217 (21.0)	220 (22.2)
t_{max} (h)[a]	1.00	2.00	2.00
$t_{1/2}$ (h)	14 (45.8)	26 (32.7)	22 (43.0)
CL/F (L/h)	3.49 (44.2)	1.59 (46.1)	2.04 (50.1)
V_z/F (L)	71.8 (39.5)	59.2 (15.8)	65.9 (17.5)

Table 7. Geometric mean (CV%) pharmacokinetic parameters of tadalafil after oral administration of a single 10 mg dose in healthy subjects and patients with renal impairment (study LVAJ).

	Group		
Parameter	Healthy subjects (N=8)	Mild renal impairment (N=5)	Moderate renal impairment (N=6)
AUC (µg*h/L)	4823 (66.7)	12657 (35.3)	17502 (45.1)
AUC(0-tn) (µg*h/L)	4735 (65.8)	11232 (38.4)	14287 (32.1)
C_{max} (µg/L)	86.5 (53.4)	113 (43.7)	142 (26.3)
t_{max} (h)[a]	18.0	36.0	48.0
$t_{1/2}$ (h)	20.0 (30.7)	44.3 (19.5)	55.4 (45.9)

Table 8. Geometric mean (CV%) pharmacokinetic parameters of total IC710 (methylcatechol glucuronide) after oral administration of a single 10 mg dose in healthy subjects and patients with renal impairment (study LVAJ).

Table 9 places Tadalafil and IC710 pharmacokinetic parameters determined in Study LVAJ alongside parameters from the presently reviewed study for the 10 mg tadalafil dose.

10 mg Tadalafil
(Geometric Mean and CV%)

Healthy Subjects	Mild Renal	Moderate Renal	End Stage Renal Failure

	(N=8) Study LVAJ	Impairment (N=3) Study LVAJ	Impairment (N=6) Study LVAJ	(N=12*) Study LVDT	
				*Poland N=6	*UK N=6
AUC Tadalafil	2868 (44.2)	6280 (46.1)	4911 (50.1)	4023 (38.2)	13749 (36.7)
Cmax Tadalafil	183 (31.2)	217 (21.0)	220 (22.2)	186 (17.2)	394 (20.8)
AUC Total IC710	4823 (66.7)	12657 (35.3)	17502 (45.1)	9983 (28.5)	15891 (34.8)
Cmax Total IC710	86.5 (53.4)	113 (43.7)	142 (26.3)	109 (35.6)	158 (33.5)

Table 9. Tadalafil and IC710 pharmacokinetic parameters determined in Study LVAJ as well as from the presently reviewed study for the 10 mg tadalafil dose.

Note in Table 9:
• For a 10 mg tadalafil dose, mean tadalafil AUC increases 1.4-fold for the subjects in the Polish cohort and 4.8-fold for subjects in the UK cohort relative to healthy subjects.
• Mean Total IC710 AUC increases 2.1-fold for the subjects in the Polish cohort and 3.3-fold for subjects in the UK cohort relative to healthy subjects.
• For a 10 mg tadalafil dose, mean tadalafil Cmax does not change for the subjects in the Polish cohort but changes 2.2-fold for subjects in the UK cohort relative to healthy subjects.
• Mean Total IC710 Cmax increases 1.3-fold for the subjects in the Polish cohort and 1.8-fold for subjects in the UK cohort relative to healthy subjects.
• The parameters for subjects with ESRF were different than for healthy subjects and for subjects with mild and moderate renal impairment receiving the same dose.

Table 10 places Tadalafil and IC710 pharmacokinetic parameters determined in Study LVAJ alongside parameters from the presently reviewed study for the 5 mg tadalafil dose.

5 mg Tadalafil
(Geometric Mean and CV%)

	Healthy Subjects (N=4) Study LVAJ	Mild Renal Impairment (N=3) Study LVAJ	Moderate Renal Impairment (N=6) Study LVAJ	End Stage Renal Failure (N=6) Study LVDT
AUC Tadalafil	1472 (25.1)	3119 (62.3)	3135 (37.5)	1633 (63.0)
Cmax Tadalafil	101 (31.2)	111 (17.4)	136 (13.2)	78.6 (21.6)
AUC Total IC710	2238 (29.3)	4955 (51.3)	8123 (32.1)	6051 (34.0)

Cmax **Total IC710**	41.3 (31.0)	53.3 (7.97)	65.7 (25.5)	64.2 (33.4)

Table 10. Tadalafil and IC710 pharmacokinetic parameters determined in Study LVAJ as well as from the presently reviewed study for the 5 mg tadalafil dose.

Note in Table 10:
• For a 5 mg tadalafil dose, mean tadalafil AUC increases 1.1-fold and mean Cmax decreases 22.2% in ESRF relative to healthy subjects.
• Mean Total IC710 AUC increases 2.7–fold and mean Cmax increases 1.6–fold relative to healthy subjects.
• The parameters for subjects with ESRF were different than for healthy subjects and for subjects with mild and moderate renal impairment.

Table 11 places Tadalafil pharmacokinetic parameters determined in Study LVBX (in healthy subjects) alongside parameters from the presently reviewed study for the 20 mg tadalafil dose.

20 mg Tadalafil
(Geometric Mean and CV%)

	Healthy Subjects **(N=16)** **Study LVBX**	**End Stage Renal Failure** **(N=6)** **Study LVDT**
AUC **Tadalafil**	6809 (24.8)	18090 (38.8)
Cmax **Tadalafil**	322 (21.2)	621 (26.6)

Table 11. Tadalafil pharmacokinetic parameters determined in Study LVBX as well as from the presently reviewed study for the 20 mg tadalafil dose.

Note in Table 11:
• There is a 2.7-fold increase in tadalafil AUC and a 1.9-fold increase in Cmax.

Table 12 places Tadalafil pharmacokinetic parameters determined in Study LVBX (in healthy subjects) alongside parameters from the presently reviewed study for the 10 mg tadalafil dose.

Note that subjects in Study LVBX were on average younger (mean(SD) age = 30 (6.8) years) than subjects in Study LVDT (10 mg dose: mean(SD) age = 50 (12.1); 5 mg dose: age = 44 (10.0)). The healthy subjects in Study LVAJ were closer in age to subjects in Study LVDT (10 mg dose: mean(SD) age = 43 (8.8); 5 mg dose: mean(SD) age = 47 (6.0)).

The following table shows the demographics of the subjects in the three studies.

Study	Population	Dose (mg)	Number of subjects	Age (years)	Body weight (kg)	Height (cm)	BMI (kg/m^2)
LVDT	Haemodialysis	5	6	44 (10.0)	81.6 (23.67)	170 (12.8)	28.0 (5.39)
		10	12	50 (12.1)	81.3 (20.03)	174 (10.6)	26.8 (4.81)
		20	6	50 (12.7)	78.4 (21.20)	174 (6.2)	25.6 (5.49)
LVAJ	Healthy	5	4	47 (6.0)	72.5 (11.21)	169 (9.4)	25.5 (2.35)
		10	8	43 (8.8)	76.0 (14.20)	176 (8.5)	24.4 (2.83)
LVBX (Part B)	Healthy	5, 10, 20	16	30 (6.8)	72.1 (11.56)	174 (10.4)	23.7 (2.52)

Source: Appendix 16.2.2 (Table 1.1) and LVAJ, LVBX reports
Arithmetic mean (SD) data are presented

10 mg Tadalafil
(Geometric Mean and CV%)

	Healthy Subjects 1 x 10 mg tablets (N=15) Study LVBX (B)	Healthy Subjects 4 x 2.5 mg tablets (N=24) Study LVBX (A)	Healthy Subjects 2 x 5 mg tablets (N=24) Study LVBX (A)	Healthy Subjects 1 x 10 mg tablets (N=24) Study LVBX (A)	End Stage Renal Failure (N=12*) Study LVDT	
					*Poland N=6	*UK N=6
AUC Tadalafil	3647 (34.0)	4120 (30.7)	4071 (32.5)	4005 (34.2)	4023 (38.2)	13749 (36.7)
Cmax Tadalafil	190 (21.7)	190 (23.4)	196 (28.5)	184 (24.3)	186 (17.2)	394 (20.8)

Table 12. Tadalafil pharmacokinetic parameters determined in Study LVBX as well as from the presently reviewed study for the 10 mg tadalafil dose.

Note in Table 12:
• Relative to the study LVBX(B), subjects in ESRF have either a 1.1-fold or a 3.8-fold increase in tadalafil AUC and either zero or a 2-fold increase in Cmax. The results are similar for all 10 mg regimens tested (LVBX(A)).

Table 13 places Tadalafil pharmacokinetic parameters determined in Study LVBX (in healthy subjects) alongside parameters from the presently reviewed study for the 5 mg tadalafil dose.

5 mg Tadalafil
(Geometric Mean and CV%)

Healthy Subjects	Mild Renal Impairment	Moderate Renal Impairment	End Stage Renal Failure

	(N=16) Study LVBX	(N=3) Study LVAJ	(N=6) Study LVAJ	(N=6) Study LVDT
AUC Tadalafil	1888 (27.5)	3119 (62.3)	3135 (37.5)	1633 (63.0)
Cmax Tadalafil	103 (25.0)	111 (17.4)	136 (13.2)	78.6 (21.6)

Table 13. Tadalafil pharmacokinetic parameters determined in Study LVBX as well as from the presently reviewed study for the 5 mg tadalafil dose.

Note in Table 13:
• Relative to healthy subjects in study LVBX, subjects with ESRF have a 14% decrease in tadalafil AUC and a 24% decrease in tadalafil Cmax.

Summary of results for 5 mg dose in ESRF relative to healthy subjects (LVAJ and LVBX):
• No change in mean tadalafil AUC (1.1-fold increase or 14% decrease)
• 22.2-24% decrease in mean tadalafil Cmax
• 2.7–fold increase in mean Total IC710 AUC
• 1.6–fold increase in mean Total IC710 Cmax

Summary of results for 10 mg dose in ESRF relative to healthy subjects (LVAJ and LVBX):
• Different studies and cohorts showed 1.1-fold, 1.4-fold, 3.8-fold and 4.8-fold increases in mean tadalafil AUC
• Different studies and cohorts showed zero, zero, 2-fold and 2.2-fold increases in mean tadalafil Cmax
• Different cohorts showed 2.1-fold or 3.3-fold increase in Total IC710 AUC
• Different cohorts showed 1.3-fold or 1.8-fold increase in mean Total IC710 Cmax

Summary of results for 20 mg dose in ESRF relative to healthy subjects (LVAJ and LVBX):
• 2.7-fold increase in mean tadalafil AUC
• 1.9-fold increase in mean Cmax.

Table 14 shows the adverse event data with respect to severity and Table 15 shows the frequency of treatment-emerge adverse events by type.

Treatment	Number of subjects studied	Subjects [%] with adverse events (all causalities)	Number of adverse events and severity (all causalities)	Subjects [%] with adverse events (drug-related[a])	Number of adverse events and severity (drug-related[a])
5 mg IC351	6	3 [50.0%]	Mild 2 Moderate 1 Severe 0 Total 3	0 [0.0%]	Mild 0 Moderate 0 Severe 0 Total 0
10 mg IC351	12	5 [41.7%]	Mild 6 Moderate 1 Severe 0 Total 7	4 [33.3%]	Mild 5 Moderate 1 Severe 0 Total 6
20 mg IC351	6	1 [16.7%]	Mild 2 Moderate 0 Severe 0 Total 2	1 [16.7%]	Mild 2 Moderate 0 Severe 0 Total 2

Source: Section 14.3.4 (Table 1)

[a] Adverse events considered to be possibly related to IC351

Table 14. Summary of Treatment-Emergent Adverse Events.

MedDRA preferred term	Number of adverse events [number of subjects with adverse event]		
	5 mg IC351 (N=6)	10 mg IC351 (N=12)	20 mg IC351 (N=6)
Headache NOS	2 [2]	3 [2]	0
Somnolence	0	3 [3]	0
Conjunctivitis	1 [1]	0	0
Dizziness	0	0	1 [1]
Electrocardiogram change NOS	0	1 [1]	0
Feeling hot	0	0	1 [1]
Total	**3 [3]**	**7 [5]**	**2 [1]**

Source: Section 14.3.4 (Table 2.1)

N = Number of subjects

NOS = Not otherwise specified

Table 15. Frequency of Treatment-Emergent Adverse Events by Type.

Note that 2 subjects receiving 5 mg tadalafil and 2 subjects receiving 10 mg tadalafil experienced headache and 3 subjects receiving 10 mg tadalafil experienced somnolence. One subject (16.7%) receiving 20 mg tadalafil experienced dizziness. No subject experienced a severe adverse event.

Table 16 and Table 17 present another side-by-side comparison of the data from studies LVBX, LVAJ, and LVDT. These tables also include information on tmax and t½ for tadalafil and Total IC710.

10 mg Tadalafil
(Geometric Mean and CV%)

	Healthy Subjects (N=15) Study LVBX (B)	Healthy Subjects (N=24) Study LVBX (A)	Healthy Subjects (N=8) Study LVAJ	Mild Renal Impair (N=3) Study LVAJ	Moderate Renal Impair (N=6) Study LVAJ	End Stage Renal Failure (N=12*) Study LVDT	
						*Poland N=6	*UK N=6
AUC Tadal	3647 (34.0)	4005 (34.2)	2868 (44.2)	6280 (46.1) 2.2-fold ↑ vs. healthy in LVAJ	4911 (50.1) 1.7-fold ↑ vs. healthy in LVAJ	4023 (38.2) 1.4-fold ↑ vs. healthy in LVAJ	13749 (36.7) 4.8-fold ↑ vs. healthy in LVAJ
Cmax Tadal	190 (21.7)	184 (24.3)	183 (31.2)	217 (21.0) 1.2-fold ↑ vs. healthy in LVAJ	220 (22.2) 1.2-fold ↑ vs. healthy in LVAJ	186 (17.2) Same as healthy in LVAJ	394 (20.8) 2.2-fold ↑ vs. healthy in LVAJ
t½ Tadal	16.7 (34.4)	17.6 (27.8)	14 (45.8)	26 (32.7)	22 (43.0)	15.2 (41.6)	24.8 (37.9)
tmax Tadal	2.0 (0.5-4.0)	2.0 (1.0-6.0)	1.0 (0.5-3.0)	2.0 (2.0-4.0)	2.0 (0.5-3.0)	4.0 (2.0-4.0)	2.04 (1.98-3.98)
AUC Total IC710			4823 (66.7)	12657 (35.3) 2.6-fold ↑ vs. healthy in LVAJ	17502 (45.1) 3.6-fold ↑ vs. healthy in LVAJ	9983 (28.5) 2.1-fold ↑ vs. healthy in LVAJ	15891 (34.8) 3.3-fold ↑ vs. healthy in LVAJ
Cmax Total IC710			86.5 (53.4)	113 (43.7) 1.3-fold ↑ vs. healthy in LVAJ	142 (26.3) 1.6-fold ↑ vs. healthy in LVAJ	109 (35.6) 1.3-fold ↑ vs. healthy in LVAJ	158 (33.5) 1.8-fold ↑ vs. healthy in LVAJ
t½ Total IC710			20.0 (30.7)	44.3 (19.5)	55.4 (45.9)	NA	NA

tmax Total IC710			18.0 (12-36)	36.0 (36-48)	48.0 (24-48)	52.4 (24-81.7)	77.5 (29.2-96.1)

Table 16. Tadalafil and Total IC710 parameters estimated in Study LVBX, LVAJ, and LVDT for the 10 mg tadalafil dose. Note that the mean (SD) age of subjects in studies LVBX, LVAJ (10 mg dose), and LVDT (10 mg dose) was 30 (6.8), 43 (8.8), and 50 (12.1). The relative change is reported with respect to Study LVAJ since the subjects were more alike in terms of demographics. All values are reported as mean (CV%) except for tmax which is median (min,max).

5 mg Tadalafil
(Geometric Mean and CV%)

	Healthy (N=16) Study LVBX	**Healthy (N=4) Study LVAJ**	**Mild Renal Impair (N=3) Study LVAJ**	**Moderate Renal Impair (N=6) Study LVAJ**	**End Stage Renal Failure (N=6) Study LVDT**
AUC Tadalafil	1888 (27.5)	1472 (25.1)	3119 (62.3) 2.1-fold ↑ vs. healthy in LVAJ	3135 (37.5) 2.1-fold ↑ vs. healthy in LVAJ	1633 (63.0) 1.1-fold ↑ vs. healthy in LVAJ
Cmax Tadalafil	103 (25.0)	101 (31.2)	111 (17.4) 1.1-fold ↑ vs. healthy in LVAJ	136 (13.2) 1.3-fold ↑ vs. healthy in LVAJ	78.6 (21.6) 22% ↓ vs. healthy in LVAJ
t½ Tadalafil	17.3 (33.5)	18 (18.3)	25 (66.9)	26 (41.7)	13.8 (51.3)
tmax Tadalafil	2.0 (1.0-6.0)	1.0 (0.5-2.0)	2.0 (1.0-3.0)	0.5 (0.5-1.0)	3.0 (2.0-4.0)
AUC Total IC710		2238 (29.3)	4955 (51.3) 2.2-fold ↑ vs. healthy in LVAJ	8123 (32.1) 3.6-fold ↑ vs. healthy in LVAJ	6051 (34.0) 2.7-fold ↑ vs. healthy in LVAJ

Cmax **Total IC710**		41.3 (31.0)	53.3 (7.97) 1.3-fold ↑ vs. healthy in LVAJ	65.7 (25.5) 1.6-fold ↑ vs. healthy in LVAJ	64.2 (33.4) 1.6-fold ↑ vs. healthy in LVAJ
t½ **Total IC710**		20 (23.9)	31 (42.8)	51 (12.8)	51.6 (52.2)
tmax **Total IC710**		20.0	24.0	42.0	55.3

Table 17. Tadalafil and Total IC710 parameters estimated in Study LVBX, LVAJ, and LVDT for the 5 mg tadalafil dose. Note that the mean (SD) age of subjects in studies LVBX, LVAJ (10 mg dose), and LVDT (5 mg dose) was 30 (6.8), 43 (8.8), and 50 (12.1). The relative change is reported with respect to Study LVAJ since the subjects in this study were more similar to subjects in LVDT in terms of demographics. All values reported as mean (CV%) except for tmax which is median (min,max).

If a 10 mg dose of tadalafil is to be used in subjects with renal impairment or End Stage Renal Failure undergoing dialysis, the dosing interval will need to be adjusted. To do so, the dosing interval will need to be such that the trough level in impaired and ESRF subjects is equivalent to the trough level in healthy subjects.

Figure 5 shows a plot of the plasma concentration of tadalafil and its metabolites in renally impaired and healthy subjects. The plasma concentration 24 hours post-dose in healthy subjects corresponds to the concentration at 48 hours in renally impaired subjects. Thus, the recommended dosing interval in these patients is 48 hours.

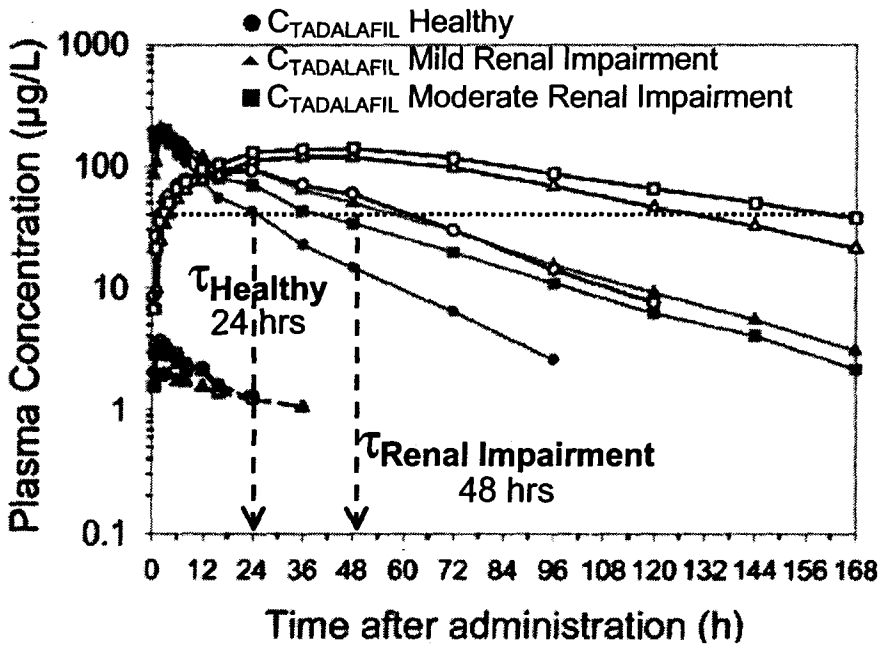


Figure 5. Plot to Estimate the Dosing Interval in Subjects with Mild and Moderate Renal Impairment.

Figure 6 shows a plot of the individual plasma concentration profiles for tadalafil in 12 patients with End Stage Renal Failure Undergoing Dialysis receiving 10 mg tadalafil. The plot of the mean response for healthy subjects receiving a 10 mg tadalafil dose is provided on the plot, as well (line labeled: Study LVBX and Study LVAJ). The horizontal line on the plot indicates the trough concentration for a 20 mg dose of tadalafil in healthy subjects. The plasma concentration 24 hours post-dose in healthy subjects corresponds to the concentration at 72 hours in renally impaired subjects. Thus, the recommended dosing interval in these patients is 72 hours.

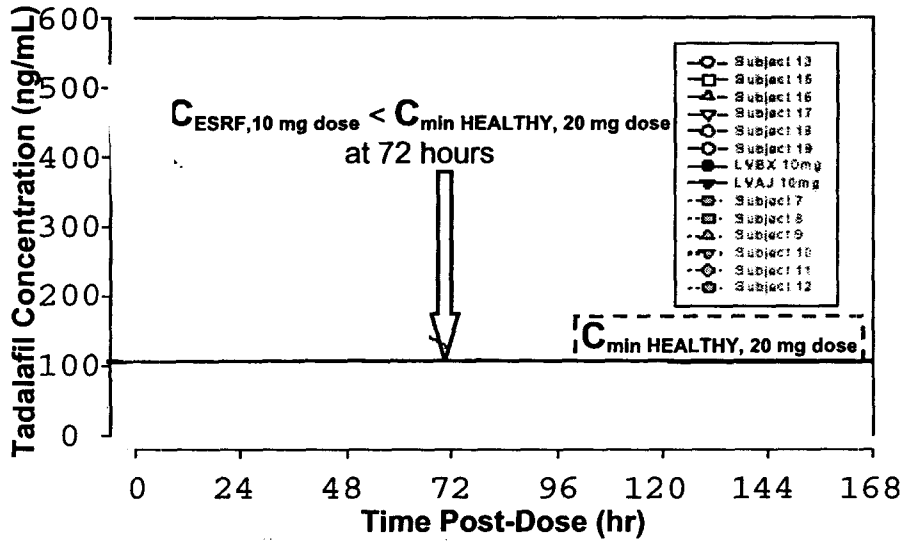


Figure 6. Plot to Estimate the Dosing Interval in Subjects with End Stage Renal Failure Undergoing Dialysis.

Other Comments

- 4 of the 6 Polish subjects at the 10 mg dose level were female; all UK subjects were male.
- The data suggest that the rate of renal elimination, rather than formation, is the rate-limiting process. Total IC710 accumulation during repeated dosing would therefore be expected to exceed accumulation of the parent compound in ESRF subjects.

Relevant Pharmacokinetics (determined in previous studies)

- Mean AUC and Cmax of tadalafil is approximately 2-fold and 1.2-fold higher in renally impaired subjects, respectively. There was no change in tmax observed.
- Tadalafil undergoes CYP3A4 mediated oxidation to a catechol metabolite.

The catechol metabolite undergoes extensive methylation and glucuronidation to form the methylcatechol and the methylcatechol glucuronide conjugate, respectively.

- The methylcatechol glucuronide is the major metabolite in human plasma and urine.

• Mean AUC of total IC710 (methylcatechol glucuronide) was approximately 3.6- fold and 2.6- fold higher in moderate and mild renally impaired subjects, respectively, and there was an increase in tmax.
• *In vitro*, the catechol and methylcatechol metabolites are highly selective for PDE5, when compared with the other PDEs.
• *In vitro*, the methylcatechol glucuronide was at least 13,000-fold less potent for PDE5 than tadalafil.
• Concentrations of methylcatechol were<10% of glucuronide concentrations.
• *In vitro*, the catechol and methylcatechol metabolites were 45-fold and 230-fold less potent for PDE5, respectively, compared with tadalafil.
• At steady state in healthy subjects, concentrations of methylcatechol glucuronide are approximately 3-fold higher than single dose values.
• In Study LVBX, individual tadalafil Cmax values for 10 mg tadalafil ranged from —— The Cmax values for both cohorts reasonably agree with these previous results. AUC increased in a dose proportional manner across the 2.5 to 20 mg dose range, but Cmax did not. Neither AUC nor Cmax increased in a dose-proportional manner in subjects with ESRF.
• In the previous submission of an NDA for tadalafil, the sponsor evaluated the pharmacokinetics of 10 mg and 20 mg doses in (Market Image Formulation) in Healthy Subjects in Study LVDK. Study LVDK showed that steady state trough levels (24 hours after dosing) of 10 mg tadalafil is approximately 90 ng/mL in healthy volunteers.

2. Study H6D-EW-LVEV
A Study to Assess the Effect of Ritonavir and Ketoconazole on the Pharmacokinetics of 20 mg IC351 (Tadalafil) in Healthy Subjects

Main Results
• Coadministration of 20 mg tadalafil with 400 mg QD ketoconazole caused the most significant CYP 3A4 drug-drug interaction with respect to increase in tadalafil exposure.
• For 400 mg QD ketoconazole, $AUC_{0\rightarrow\infty}$ increased 4.1-fold on average and the most extreme change was 5.9-fold. In addition, Cmax increased 1.2-fold on average and the most extreme change was 1.9-fold.
• The results are consistent with an earlier study (LVAZ) of coadministration of 10 mg tadalafil and 200 mg ketoconazole; there, AUC increased 2-fold and Cmax increased 1.15-fold.
•When tadalafil was co-administered with 400 mg QD ketoconazole, the geometric mean CL/F for tadalafil was reduced by approximately 76%.
• AUC and Cmax of tadalafil's major metabolite, methylcatechol glucuronide, was lower after coadministration with ketoconazole (25% decrease in AUC, 62% decrease in Cmax) or ritonavir (200 mg BID regimen: 66% decrease in AUC, 80% decrease in Cmax) relative to dosing tadalafil alone.
• Administration of 200 mg BID ritonavir resulted in a mean 2.6-fold increase in AUC and no change in mean Cmax.
• Administration of 200 mg BID ritonavir resulted in a mean 2-fold increase in tadalafil's half-life and the geometric mean CL/F for tadalafil was reduced by approximately 60%.

• The drug interaction study with 600 mg BID ritonavir is difficult to interpret given the small sample size. Because 600 mg BID ritonavir was poorly tolerated, five of the 8 subjects were withdrawn after receiving ritonavir but prior to receiving a coadministered dose of tadalafil. Only 3 of the 8 subjects receiving 600 mg BID ritonavir remained in the study until tadalafil dosing on Day 3 (and discontinued after Day 3) because of ritonavir-related adverse events.

• The 3 subjects who remained in the 600 mg BID ritonavir interaction study long enough to receive both ritonavir and tadalafil demonstrated the following.

*a smaller change in tadalafil AUC relative to when tadalafil dosed alone (mean: 1.7-fold increase) than for the 200 mg BID study (mean: 2.6-fold increase)

*a 14% decrease in Cmax, whereas the 200 mg BID ritonavir interaction study demonstrated no change in Cmax

*no change in half-life, whereas the 200 mg BID ritonavir interaction study demonstrated a 2-fold increase in half-life

*a 3.33-fold increase in tmax, whereas the 200 mg BID ritonavir interaction study demonstrated a 1.33-fold increase in tmax.

*If the results of the 600 mg BID ritonavir interaction study are believable, they suggest that the effect of the interaction between 20 mg tadalafil and 600 mg BID ritonavir may be conservative with respect to safety.

Note, that although the parameters for the 3 subjects who received 600 mg BID ritonavir are compared above to those measured in subjects completing the 200 mg BID ritonavir interaction study, this is not a "fair" comparison given that subjects on the 600 mg BID ritonavir arm only received 1 day of coadministration of tadalafil with ritonavir, while subjects on the 200 mg BID ritonavir arm received 7 days of coadministration.

• The discrepancy in the results of the studies of 200 mg vs 600 mg BID ritonavir may:

1. Be an artefact of the small sample size for the 600 mg ritonavir arm (N=3)
2. Reflect a difference in the pharmacokinetic profile between subjects who were able to tolerate 600 mg BID ritonavir and subjects who could not tolerate 600 mg BID ritonavir.
3. Reflect a change in the balance between CYP 3A4 inhibition and induction for these strengths; CYP 3A4 inhibitors can also induce CYP 3A4 expression
4. Reflect the difference in the duration of inhibition; the 200 mg BID ritonavir study involved 7 days of tadalafil-ritonavir coadministration, while the 600 mg BID ritonavir study involved only 1 day of tadalafil-ritonavir coadministration.

• Back pain was frequently reported, with 42.8%, 37.5%, and 25% of subjects receiving 20 mg tadalafil alone, 200 mg BID ritonavir, and 400 mg QD ketoconazole reporting back ache, respectively.

• Myalgia was reported by 2/28 (7.1%), 1/8 (12.5%), and 1/12 (8.3%) of subjects receiving 20 mg tadalafil alone, 200 mg BID ritonavir, and 400 mg ketoconazole, respectively.

• The onset of back pain and myalgia considered to be related to administration of tadalafil was generally within 48 hours of dosing with tadalafil.

• The sponsor submitted a second analysis of the ritonavir data (received 8/8/03). The sponsor asserted that the "worst case scenario" for potent CYP 3A inhibition is that ritonavir 600 mg BID increases tadalafil exposure to a similar extent as 400 mg ketoconazole QD. Several pieces of evidence were provided.

Evidence from the literature included:
(1) in vitro concentration-response data has shown that ritonavir is nearly as potent as ketoconazole for CYP 3A inhibition
(2) based on the proportionality in inhibitory response for saquinavir AUC following 600 mg BID ritonavir relative to 300 mg BID ritonavir, the inhibitory response in vivo—with respect to AUC—at 600 mg BID should almost triple the response observed with 200 mg BID. (It is unclear how this assertion was meant to support the sponsor's application. A 3-fold increase in tadalafil exposure upon dosing with 600 mg BID ritonavir relative to 200 mg BID ritonavir would correspond to prediction of a 3 x 2.6-fold increase, or a 7.8-fold increase in AUC.)
(3) The effect of ritonavir on Cmax is relatively small for most compounds.
(4) Ritonavir is known to inhibit multiple drug-metabolizing enzymes, including CYP 3A, CYP 2D6, and CYP 2C. A significant component of its inhibitory effect is due to inhibition of first-pass metabolism. Long term administration of high dose ritonavir has been associated with a reduction in its own exposure due to induction of CYP 3A. Therefore, the inhibitory effect of ritonavir will decrease with time and dose.
(5) Tadalafil is a low clearance drug (apparent oral clearance = 2.48 L/hr). Moderate to high clearance drugs are more susceptible to effects of strong inhibitors on first-pass and systemic metabolism than low clearance drugs.

Evidence from the data in Study LVEV included:
(1) By means of simulations using the same study design, sample size, and sampling strategy, Study LVEV was replicated 200 times to characterize the expected distribution of possible AUC outcomes. The simulation model accounted for inhibition of first-pass metabolism as well as effects on systemic clearance of tadalafil. Worst-case assumptions for the influence of key model parameters—such as the effect on first-pass and the influence of ritonavir on inhibitory constant and protein binding were tested within the simulation environment. The median predicted tadalafil AUC ratio in the presence and absence of 200 mg BID ritonavir was 2.2—the same value as reported in Study LVEV. The median and maximum AUC ratio predicted (presence of 600 mg BID ritonavir/absence of BID ritonavir) were 3.3 and 4.0, respectively. This inhibitory response is slightly less than that for ketoconazole 400 mg/day.

Background
Tadalafil undergoes extensive oxidative metabolism via cytochrome P450 3A4 (CYP3A4) to a catechol that is metabolized further to a methylcatechol (IC710). The major metabolite in plasma is the glucuronide conjugate of this methylcatechol, and was assayed by the sponsor as the total methylcatechol in hydrolysed plasma (total IC710).

The potential interaction between ketoconazole, a known CYP3A4 inhibitor, and a 10 mg dose of tadalafil has previously been investigated (Study LVAZ). In that Study, tadalafil plasma concentrations increased in the presence of ketoconazole (200 mg administered once-daily (QD)), such that the geometric mean AUC increased 2-fold than when tadalafil was administered alone.

Objective

Primary Objective

Determine the effects of ritonavir and ketoconazole on the pharmacokinetics of 20 mg tadalafil. Tadalafil 20 mg was co-administered with ketoconazole (400 mg QD) or with ritonavir (200 or 600 mg twice-daily (BID)).

Secondary Objective

Further assess the safety and tolerability of single 20 mg oral doses of tadalafil when administered alone and following administration of ritonavir or ketoconazole.

Design

Study LVEV was a randomized, open-label study conducted in two parts (A and B). The plan was as follows:

Part A: Ritonavir interaction study
- Group 1: 200 mg BID ritonavir capsules (2 x 100 mg), N=8
- Group 2: 600 mg BID ritonavir capsules (6 x 100 mg), N=8

Part B: Ketoconazole interaction study
- 400 mg QD ketoconazole tablets (2 x 200 mg), N=12

Part A examined the interaction of tadalafil with two dose levels of ritonavir and Part B examined the interaction of tadalafil with ketoconazole. Each of Part A and Part B of Study LVEV had 2 periods. In Period 1, tadalafil 20 mg was dosed alone starting on study Day 1. In Period 2, the plan was to dose the CYP 3A4 inhibitor starting on study Day 1 and continue to dose until Day 10. Additionally, in Period 2, tadalafil 20 mg dosing began two days after the start of dosing of the CYP 3A4 inhibitor (Study Day 3). The purpose of dosing the CYP3A4 inhibitor 2 days before commencing tadalafil dosing was to ensure inhibition of CYP3A4. A washout interval of 10 to 14 days between Period 1 and Period 2 was performed to eliminate any residual tadalafil from Treatment Period 1 prior to dosing in Treatment Period 2.

Healthy males between 18 and 65 years old were included in the study.

Water was not permitted from the time of dosing until 2 hours postdose on each tadalafil dosing occasion. Alcohol was actively discouraged from 48 hours prior to the first dosing occasion. Grapefruit, grapefruit juice and grapefruit-containing products were not allowed from 7 days prior to the first dose of tadalafil until after the final pharmacokinetic blood sampling occasion in Treatment Period 2. Smoking was not allowed on any day when tadalafil was administered, and for 1 hour before each vital signs measurement. For the remainder of the study, subjects were not to smoke more than 10 cigarettes or equivalent per day. Prescribed medication was not permitted for 14 days before the first dose of tadalafil, through to the final follow-up visit. Over-the-counter medication was not permitted for 7 days before the first dose of tadalafil, through to the final follow-up visit (except occasional paracetamol or ibuprofen use).

Plasma samples were analyzed for tadalafil, total IC710 and IC710.

Planned Analyses

• The sponsor's pharmacokinetic analyses consisted of a non-compartmental assessment of tadalafil and total IC710 plasma concentration-time data. Cmax and tmax were directly determined from the observed plasma concentration-time profiles.

• All subjects who received at least one dose of tadalafil, and with evaluable pharmacokinetic data, were included in the sponsor's summary statistics and only subjects who had data for both treatment periods were included in the statistical analysis. For withdrawn subjects, all available pharmacokinetic data were listed up to the point of withdrawal.

• Absence of a drug interaction was to be concluded if the upper 90% confidence limit for the ratio of AUC(0-8) and Cmax for tadalafil co-administered with ritonavir/ketoconazole relative to tadalafil administered alone was less than two. A one-sided hypothesis was used as only an increase in exposure was expected when tadalafil was co-administered with ritonavir or ketoconazole.

• As the variance for all pharmacokinetic parameters (except tmax) increases as the mean increases, these parameters were log-transformed (base e) prior to analysis and were analysed using a mixed model of the form:
RESPONSE = SUBJECT + TREATMENT + RANDOM ERROR
In the above model, the term 'Subject' was fitted as a random effect and the term 'Treatment' was fitted as a fixed effect. The term 'Treatment' was used to distinguish between the Period 1 and Period 2 treatments. Residual plots were produced to assess the distribution of the data and the adequacy of the model. There was no evidence within the plots to suggest significant departures from normality, and therefore, an additional analysis was not required.

• Statistical analysis was used to determine estimates of the inter-subject (between) and intra-subject (within) variability, expressed as CV%, in the pharmacokinetic parameters of tadalafil and total IC710.

Ritonavir Drug Interaction Study Results

Parent Compound

Sixteen subjects were recruited and entered Part A of the study. All eight subjects who received 200 mg BID ritonavir in Treatment Period 2 (Subjects 1 to 8) completed the study. Five of the eight subjects receiving ritonavir 600 mg bid withdrew before Day 3 (when ritonavir was to be coadministered with tadalafil) due to adverse events considered related to ritonavir. The remaining 3 subjects were withdrawn prior to dosing with 600 mg bid ritonavir on Day 4. Two of the three subjects were withdrawn due to adverse events considered related to ritonavir. One of the two had headache, which could possibly be related to tadalafil. The remaining subject was withdrawn as a precautionary measure. Therefore, no subject who received 600 mg ritonavir BID completed the study.
Twelve subjects were recruited and entered Part B of the study. Eleven of these subjects completed the study: the one withdrawal was due to personal reasons. Therefore, of a total of 28 subjects, 19 subjects completed the study as planned.

Although the actual age range of participants was 19-54, all but two subjects (one, aged 54, who entered the 600 mg bid ritonavir arm and another, aged 50, who entered the ketoconazole arm) was between the ages of 19 and 33. Subject 8 was of mixed race (Caucasian/Asian), Subjects 17 and 25 were Afro-Caribbean (origin for Subject 25 recorded on CRF as being 'Black African'); all other subjects were Caucasian.
For several subjects, back pain occurred on Day 2 in Treatment Period 1, therefore clinical laboratory evaluations to test for myalgia should have been performed on Day 4 (i.e. 48 hours later). However, some of these subjects were not able to attend on Day 4: for these subjects, the tests were performed either at discharge on Day 3 or on Day 5.

Using estimates of the intra-subject variability from a previous study (LVAZ), and with eight subjects in each part of the study completing, the present study had at least 90% power to detect a two-fold increase in AUC and Cmax . The assumed intra-subject coefficients of variation were 10.9% for Cmax and 25.3% for AUC. This assumed a one-sided type I error rate of 5%. The power of the ritonavir 600 mg arm is likely reduced significantly by withdrawal. Thus, it was not possible to make a statistical comparison of pharmacokinetic parameters between this treatment to when tadalafil was administered alone.

Arithmetic mean (SEM) plasma concentration-time profiles of tadalafil following oral doses of 20 mg IC351 (tadalafil) in the presence and absence of ritonavir are presented in Figure 1.

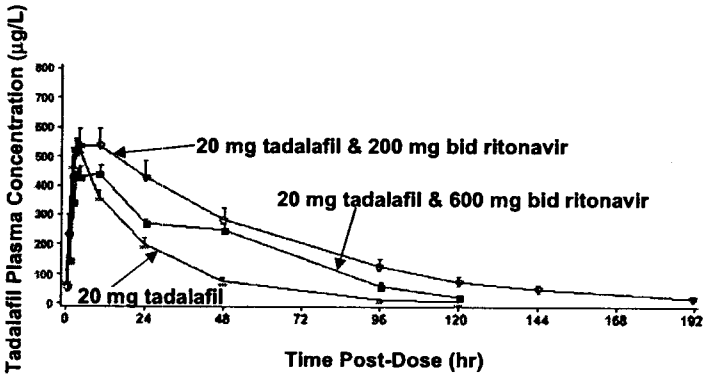


Figure 1. Arithmetic Mean (±SEM) Plasma Concentration-Time Profiles of Tadalafil Following Oral Administration of a Single 20 mg Dose Alone (N=16) and in Combination with 200 mg BID Ritonavir (N=8) or 600 mg BID. Ritonavir (N=3).

Following co-administration of tadalafil with 200 mg BID ritonavir, tadalafil plasma concentrations were increased compared to when tadalafil was administered alone. There was little effect on the range of Cmax values: ——— compared to ——— when tadalafil was administered alone. Tadalafil was quantifiable in plasma up to the last blood sampling time (192 hours) for all subjects co-administered tadalafil and 200 mg b.d. ritonavir, but for only 3 of 16 subjects following administration of tadalafil alone. The pharmacokinetic parameters of IC351 (tadalafil) from Part A of the study are summarized in Table 1.

Parameter	20 mg IC351 (N=16)	20 mg IC351 & 200 mg b.d. ritonavir (N=8)	20 mg IC351 & 600 mg b.d. ritonavir (N=3)
AUC(0-∞) (µg.h/L)	12850 (36.4)[a]	33033 (40.3)	22418 (13.7)
AUC(0-t_{last}) (µg.h/L)	12358 (35.6)	32200 (38.4)	22230 (14.4)
C_{max} (µg/L)	561.976 (23.2)	533.887 (25.3)	471.461 (7.3)
t_{max} (h)[b]	3.00	4.00	10.00
t½ (h)[c]	16.4	31.9	17.2
CL/F (L/h)	1.56 (36.4)[a]	0.605 (40.3)	0.892 (13.7)
V_z/F (L)	36.9 (18.7)[a]	27.9 (24.2)	22.2 (36.1)

Source: Section 14.2.2 (Table 2.1)
N = Number of subjects
[a] N=14
[b] Median (min-max) data
[c] Geometric mean (min-max) data
µg/L is equivalent to ng/mL

Table 1. Geometric Mean (CV%) of Pharmacokinetic Parameters of IC351 (tadalafil) Following Oral Administration of a Single 20 mg Tadalafil Dose Alone or in Combination with 200 or 600 mg BID Ritonavir.

Table 2 summarizes the relative change in pharmacokinetic parameters for the ritonavir interaction study versus dosing tadalafil alone.

	200 mg dose (N=8)	**600 mg dose (N=3)**
AUC ∝ F/CL	↑ (2.6-fold)	↑ (1.7-fold)
Cmax ∝ F/V (ka, k)	←→	↓ (0.84 of dosing alone)
tmax ∝ ka, k	↑ (1.33x & more variable)	↑ 3.33-fold
t½ ∝ V/CL	↑ (2-fold)	←→
CL/F ∝ CLint, fu, Q_H	↓ (0.4 of dosing alone)	↓ (0.6 of dosing alone)
Vz/F ∝ Vp, fu/fuT	↓ (0.8 of dosing alone)	↓ (0.6 of dosing alone)

Table 2. Relative Change in Pharmacokinetic Parameters for the Ritonavir Interaction Study Relative to Dosing Tadalafil Alone.

In the presence of 200 mg BID ritonavir, there was a 2.6-fold increase in AUC, the geometric mean CL/F decreased approximately by 60% and Vz/F decreased by 20%. This decrease in CL/F and V/F was reflected by a two-fold increase in geometric mean half-life: 31.9 hours compared to 16.4 hours when tadalafil was administered alone. Cmax did not change—suggesting that ritonavir does not affect F or gut metabolism—but tmax increased 1.33-fold, suggesting that ritonavir affects the rate of absorption.

The results were similar for the 600 mg ritonavir dose qualitatively, but differed quantitatively. AUC was increased less by ritonavir 600 mg BID (1.7-fold) versus ritonavir 200 mg BID (2.6-fold). This reflects a smaller Cmax for the 600 mg ritonavir interaction study (16% decrease) relative to when tadalafil was dosed alone.

The most striking difference between the effect of the 200 mg and 600 mg doses of ritonavir is on tadalafil's tmax and t1/2. Although both regimens yield an increase in tmax, it appears that the 600 mg bid dose of ritonavir has a more considerable influence on tmax (3.33-fold increase) than the 200 mg dose (1.33-fold increase). A two-fold increase in t1/2 was observed for the 200 mg dose of ritonavir, but there was no change in t1/2 observed for the 600 mg dose. This, like the difference in the magnitude of the effect on Vz/F for the ritonavir doses (Vz/F is decreased by 20% and 40% when 200 mg and 600 mg ritonavir BID are dosed, respectively), and the discrepancy in the effect on AUC and Cmax, may be an artefact of the small sample size for the 600 mg ritonavir arm. It may also reflect a difference in pharmacokinetic profile between subjects who were able to tolerate 600 mg BID ritonavir and subjects who could not tolerate 600 mg BID ritonavir. CYP 3A4 inhibitors can also induce CYP 3A4 expression. The discrepancy in the effect of ritonavir on tadalafil's PK parameters for the 200 mg and 600 mg doses may reflect a change in the balance between CYP 3A4 inhibition and induction for these strengths.

Note, that it is unexpected that the coefficients of variation are lower for the 600 mg bid ritonavir arm compared to the 200 mg arm or the arm studying tadalafil alone. One would expect the results to be more variable given that fewer subjects were studied.

The results of the statistical comparison of select pharmacokinetic parameters of tadalafil (IC351) are summarized in Table 3. There is a statistically significant change in AUC caused by coadministration with 200 mg BID ritonavir. Note that the sponsor's reporting of 90% confidence intervals may underestimate drug effect relative to a 95% CI.

Parameter	Ratio of geometric LS means (IC351 & 200 mg b.d. ritonavir: IC351 alone)	90% confidence limits for the ratio
AUC(0-∞)	2.24	1.86, 2.71
C_{max}	0.980	0.822, 1.17
t_{max} (h)[a]	3.00	0.467, 6.00

Source: Section 14.2.2 (Table 1.1)
Analysis only includes Period 1 data (IC351 alone) from the eight subjects who received IC351 and 200 mg b.d. ritonavir in Period 2
[a] Median difference (IC351 & 200 mg b.d. ritonavir - IC351 alone) and 90% confidence limits
µg/L is equivalent to ng/mL

Table 3. Statistical Comparison of the Primary Pharmacokinetic Parameters of Tadalafil Following Oral Administration of a Single 20 Dose Alone and in Combination with 200 mg BID Ritonavir.

The sponsor claims that the limited results obtained in the 3 subjects who received 600 mg BID ritonavir with tadalafil were consistent with those seen with the 200 mg BID dosing regimen.

Metabolites