

Pharmacokinetic parameters of total IC710 (the metabolites of tadalafil) from Part A of the study are summarized in Table 4.

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)	10123 (28.3)	3673 (52.0)	4167 (29.3)
AUC(0-t <sub>last</sub> ) (µg.h/L)	10021 (28.4)	3427 (47.6)	4043 (28.3)
C <sub>max</sub> (µg/L)	154.924 (29.9)	32.520 (36.5)	42.531 (14.2)
t <sub>max</sub> (h) <sup>a</sup>	24.00 ( )	47.93 ( )	48.00 ( )
t <sub>1/2</sub> (h) <sup>b</sup>	21.9 ( )	33.6 ( )	29.2 ( )
MR	0.787 (36.0) <sup>c</sup>	0.111 (28.7)	0.186 (15.1)

Source: Section 14.2.2 (Table 3.1)

N = Number of subjects

<sup>a</sup> Median (min-max) data

<sup>b</sup> Geometric mean (min-max) data

<sup>c</sup> N=14

µg/L is equivalent to ng/mL

**Table 4. Geometric Mean (CV%) Pharmacokinetic Parameters of Total IC710 Following Oral Administration of a Single 20 mg Dose Alone or in Combination with 200 or 600 mg b.d. Ritonavir .**

Table 5 describes the relative change in pharmacokinetic parameters for the metabolite observed in the ritonavir interaction studies versus dosing tadalafil alone.

	200 mg dose (N=8)	600 mg dose (N=3)
AUC ∝ F/CL	↓ (0.36 of dosing alone)	↓ (0.4 of dosing alone)
C <sub>max</sub> ∝ F, V (k <sub>a</sub> , k)	↓ (0.2 of dosing alone)	↓ (0.27 of dosing alone)
t <sub>max</sub> ∝ k <sub>a</sub> , k	↑ (2-fold)	↑ (2-fold)
t <sub>1/2</sub> ∝ V/CL	↑ (1.5-fold)	↑ (1.33-fold)
Metabolite ratio	↓ (0.14 of dosing alone)	↓ (0.24 of dosing alone)

**Table 5. Relative Change in Pharmacokinetic Parameters of IC710 for the Ritonavir Interaction Study Relative to Dosing Tadalafil Alone.**

Following co-administration of tadalafil with 200 mg BID ritonavir, total IC710 plasma concentrations were lower compared to when tadalafil was administered alone: C<sub>max</sub> values ranged from \_\_\_\_\_ compared to \_\_\_\_\_, respectively. In the presence of 200 mg BID ritonavir, the geometric mean half-life of total IC710 was longer: 33.6 hours compared to 21.9 hours, respectively. The results of the statistical comparison of selected pharmacokinetic parameters of tadalafil are summarized in the following Table 6.

Parameter	Ratio of geometric LS means (IC351 & 200 mg b.d. ritonavir: IC351 alone)	90% confidence limits for the ratio
AUC(0-∞)	0.341	0.257, 0.452
C <sub>max</sub>	0.219	0.169, 0.283
t <sub>max</sub> (h) <sup>a</sup>	18.9	11.9, 23.9

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

<sup>a</sup> Median difference (IC351 & 200 mg b.d. ritonavir - IC351 alone) and 90% confidence limits  
μg/L is equivalent to ng/mL

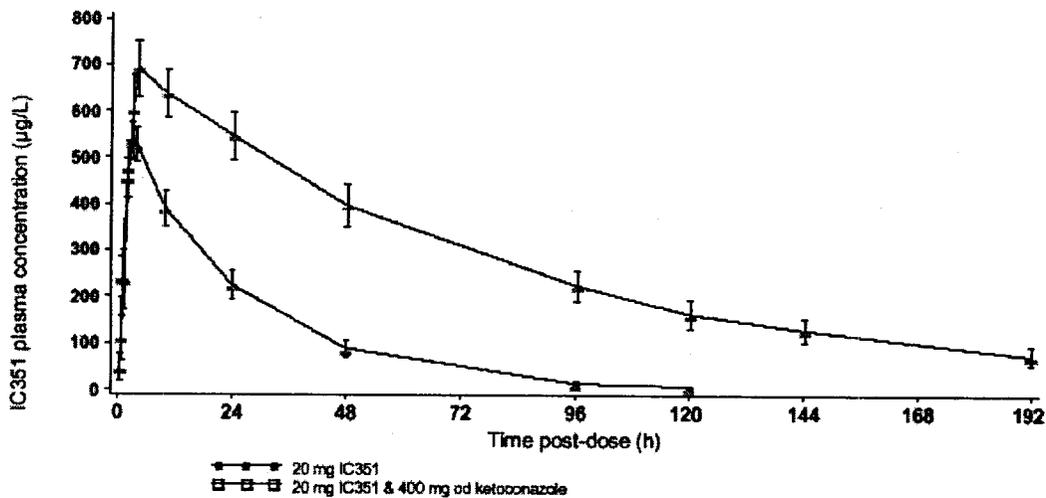
**Table 6. Statistical Comparison of the Primary Pharmacokinetic Parameters of Total IC710 Following Oral Administration of a Single 20 mg Tadalafil (IC 351) Dose Alone and in Combination with 200 mg BID Ritonavir. All the differences are statistically significant.**

Exposure to total IC710 metabolite was reduced in the presence of 200 mg BID ritonavir, with AUC(0-8) being approximately 66% lower compared to when tadalafil was administered alone. Similarly, C<sub>max</sub> for total IC710 when tadalafil was co-administered with 200 mg BID ritonavir was approximately 78% lower compared to when tadalafil was administered alone, with the median t<sub>max</sub> for total IC710 occurring 19 hours later compared to when tadalafil was administered alone. All these differences were statistically significant.

The mean metabolic ratio (total IC710: tadalafil), in terms of AUC(0-8), was approximately 0.8 following administration of tadalafil alone, and 0.1 following co-administration of tadalafil with 200 mg BID ritonavir.

### Ketoconazole Drug Interaction Study Results

Arithmetic mean (SEM) plasma concentration-time profiles of tadalafil following oral doses of 20 mg tadalafil in the presence and absence of ketoconazole are presented in Figure 2.



**Figure 2. Arithmetic Mean ( $\pm$ 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.**

Following co-administration of tadalafil with 400 mg QD ketoconazole, tadalafil plasma concentrations were higher compared to when tadalafil was administered alone. C<sub>max</sub> values ranged from  $\sim$   $\mu$ g/L compared to  $\sim$   $\mu$ g/L, respectively. The pharmacokinetic parameters of tadalafil in this case are summarized in Table 7.

Parameter	20 mg IC351 (N=12)	20 mg IC351 & 400 mg o.d. ketoconazole (N=12)
AUC(0- $\infty$ ) ( $\mu$ g.h/L)	13006 (43.9)	53524 (49.2)
AUC(0-t <sub>last</sub> ) ( $\mu$ g.h/L)	12945 (44.4)	48231 (42.4)
C <sub>max</sub> ( $\mu$ g/L)	548.156 (24.0)	669.731 (29.9)
t <sub>max</sub> (h) <sup>a</sup>	3.00 ( $\sim$ )	4.00 ( $\sim$ )
t <sub>1/2</sub> (h) <sup>b</sup>	15.7 ( $\sim$ )	50.7 ( $\sim$ )
CL/F (L/h)	1.54 (43.9)	0.374 (49.2)
V <sub>z</sub> /F (L)	34.8 (24.7)	27.3 (32.3)

Source: Section 14.2.2 (Table 2.2)

N= Number of subjects

<sup>a</sup> Median (min-max) data

<sup>b</sup> Geometric mean (min-max) data

$\mu$ g/L is equivalent to ng/mL

**Table 7. Geometric Mean (CV%) Pharmacokinetic Parameters of IC351 (Tadalafil) Following Oral Administration of a Single 20 mg IC351 (Tadalafil) Dose Alone or in Combination with 400 mg q.d. Ketoconazole.**

Table 8 lists the relative change in tadalafil pharmacokinetic parameters for the coadministration of 400 mg QD ketoconazole and 20 mg tadalafil relative to when tadalafil was dosed alone.

	400 mg ketoconazole
AUC $\propto$ F/CL	$\uparrow$ (4.1-fold)
C <sub>max</sub> $\propto$ F, V (ka, k)	$\uparrow$ (1.2-fold)
t <sub>max</sub> $\propto$ ka, k	$\uparrow$ (1.33-fold)
t <sub>1/2</sub> $\propto$ V/CL	$\uparrow$ (3.2-fold)
CL/F $\propto$ CL <sub>int</sub> , fu, Q <sub>H</sub>	$\downarrow$ (0.24 of dosing alone)
V <sub>z</sub> /F $\propto$ V <sub>p</sub> , fu/fuT	$\downarrow$ (0.78 of dosing alone)

**Table 8. Relative Change in Tadalafil Pharmacokinetic Parameters for the Ketoconazole Interaction Study Relative to Dosing Tadalafil Alone.**

In the presence of 400 mg QD ketoconazole, geometric mean CL/F decreased approximately 76% and V<sub>z</sub>/F decreased 22%. This decrease in CL/F was reflected by an increase in geometric mean half-life: 50.7 hours compared to 15.7 hours, respectively. Table 9 shows the statistical significance of these results.

Parameter	Ratio of geometric LS means (IC351 & 400 mg o.d. ketoconazole: IC351 alone)	90% confidence limits for the ratio
AUC(0-∞)	4.12	3.70, 4.58
C <sub>max</sub>	1.22	1.11, 1.35
t <sub>max</sub> (h) <sup>a</sup>	3.03	0.500, 6.00

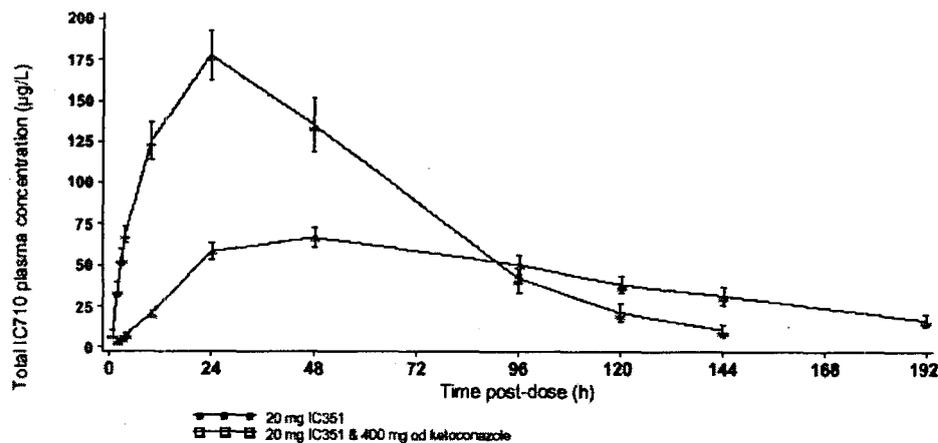
Source: Section 14.2.2 (Table 1.2)

<sup>a</sup> Median difference (IC351 & 400 mg o.d. ketoconazole - IC351 alone) and 90% confidence limits µg/L is equivalent to ng/mL

**Table 9. Statistical Comparison of the Primary Pharmacokinetic Parameters of IC351 (Tadalafil) Following Oral Administration of a Single 20 mg Tadalafil Dose Alone and in Combination with 400 mg QD Ketoconazole.**

AUC(0-8) was 4.1-fold greater when tadalafil was co-administered with 400 mg QD ketoconazole compared to when tadalafil was administered alone. The most extreme relative change observed was 5.9-fold. C<sub>max</sub> was 1.2-fold higher when tadalafil was co-administered with 400 mg QD ketoconazole, with the most extreme change observed 1.9-fold. Median t<sub>max</sub> occurred significantly later (3 hours later) compared to when tadalafil was dosed alone.

Arithmetic mean ( SEM) plasma concentration-time profiles of total IC710 (tadalafil metabolites) following oral doses of 20 mg tadalafil in the presence and absence of 400 mg QD ketoconazole are presented in Figure 3.



**Figure 3. Arithmetic Mean (±SEM) Plasma Concentration-Time Profiles of Total IC710 Following Oral Administration of a Single 20 mg Dose Alone (N=12) and in Combination with 400 mg QD Ketoconazole (N=12).**

Pharmacokinetic parameters of total IC710 from Part B of the study are summarized in Table 10.

Parameter	20 mg IC351	20 mg IC351 & 400 mg o.d. ketoconazole
	(N=12)	(N=12)
AUC(0-∞) (µg.h/L)	11058 (36.8)	8362 (29.5) <sup>a</sup>
AUC(0-t <sub>last</sub> ) (µg.h/L)	10939 (36.6)	7427 (35.3)
C <sub>max</sub> (µg/L)	172.726 (27.7)	65.149 (35.8)
t <sub>max</sub> (h) <sup>b</sup>	24.00 ( — )	47.88 ( — )
t <sub>1/2</sub> (h)	20.7 ( — )	55.0 ( — )
MR	0.850 (33.3)	0.170 (35.1) <sup>a</sup>

Source: Section 14.2.2 (Table 3.2)

N = Number of subjects

<sup>a</sup> N=11

<sup>b</sup> Median (min-max) data

<sup>c</sup> Geometric mean (min-max) data

µg/L is equivalent to ng/mL.

**Table 10. Geometric Mean (CV%) Pharmacokinetic Parameters of Total IC710 Following Oral Administration of a Single 20 mg IC351 (Tadalafil) Dose Alone or in Combination with 400 mg QD Ketoconazole.**

Table 11 lists the relative change in Total IC710 pharmacokinetic parameters for the coadministration of 400 mg QD ketoconazole and 20 mg tadalafil relative to when tadalafil was dosed alone.

	400 mg ketoconazole
AUC ∝ F/CL	↓ (0.75 of dosing alone)
C <sub>max</sub> ∝ F, V (ka, k)	↓ (0.38 of dosing alone)
t <sub>max</sub> ∝ ka, k	↑ (2-fold)
t <sub>1/2</sub> ∝ V/CL	↑ (2.7-fold)
Metabolic Ratio	↓ (0.2 of dosing alone)

**Table 11. Relative Change in Pharmacokinetic Parameters for IC710 in the Ketoconazole Interaction Study Relative to when Tadalafil Dosed Alone.**

Following co-administration of tadalafil with 400 mg QD ketoconazole, total IC710 plasma concentrations were lower compared to when tadalafil was administered alone: C<sub>max</sub> values ranged from — µg/L compared to — µg/L, respectively. Geometric mean half-life of total IC710 was longer, 55.0 hours compared to 20.7 hours when tadalafil was administered alone. Exposure to total IC710 metabolite was reduced in the presence of 400 mg QD ketoconazole, with AUC approximately 25% lower and C<sub>max</sub> approximately 62% lower compared to when tadalafil was administered alone. The median t<sub>max</sub> for total IC710 increases 2-fold. All these differences were statistically significant.

The mean metabolic ratio (total IC710: tadalafil), in terms of AUC(0-8), was approximately 0.9 following administration of tadalafil alone, and 0.2 following co-administration of tadalafil with 400 mg QD ketoconazole.

For both CYP3A4 inhibitors, the upper 90% confidence limit for ratio (tadalafil and CYP3A4 inhibitor: tadalafil alone) of AUC(0-8) was greater than two. On the basis of this predefined criteria, the null hypothesis of the absence of an interaction with either CYP3A4 inhibitor was rejected.

### Results: Adverse Events

Table 12 lists the frequency of adverse events.

MedDRA term	Number of adverse events [number of subjects with adverse event]			
	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 <sup>a</sup> )	20 mg IC351 & 400 mg o.d. ketoconazole (N=12)
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]			
<b>Total</b>	<b>51 [21]</b>	<b>9 [6]</b>	<b>5 [2]</b>	<b>32 [10]</b>

Source: Section 14.3.4 (Table 2.2)

N= Number of subjects

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

<sup>a</sup> Three subjects received IC351

NOS = Not otherwise specified

**Table 12. Frequency of Treatment-Emergent Drug-Related Adverse Events by Type.**

Headache was the most frequently reported adverse event considered related to tadalafil—16/28 of subjects (57%) receiving tadalafil alone, 2/8 of subjects (25%) receiving 200 mg BID ritonavir, 1/8 of subjects (12.5%) receiving 600 mg BID ritonavir and 9/12 (75%) of subjects receiving 400 mg ketoconazole reported headache. Back pain was also 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.

### Relevant Pharmacokinetics/Reference Information

- Results with cultured human hepatocytes indicated that tadalafil produces both mechanism-based inhibition of CYP3A activity and induction of CYP3A protein expression.
- The reviewer of the original submission of this NDA reported that C<sub>max</sub> changes nonlinearly with doses greater than 10 mg although AUC has linear kinetics to 20 mg.
- Note that ritonavir has no influence on P-glycoprotein and that it is an inhibitor of a number of additional CYP isoforms, including CYP2C9, CYP2C19 and CYP2D6.
- Once-daily administration of 20 mg tadalafil for 10 days resulted in a mean C<sub>max</sub> value of 322 µg/L; the highest individual plasma concentration was 719 µg/L.
- Variability in t<sub>max</sub> of tadalafil was noted in the review of the original submission of this NDA. In a study comparing tablet strengths (4 x 2.5mg vs 2 x 5 mg vs 1 x 10 mg) of tadalafil and investigating the dose proportionality of tadalafil pharmacokinetics when administered at four dose levels (2.5, 5, 10 and 20 mg; N=16 at each level), individual t<sub>max</sub> values ranged from 0.5 to 6 hours across all doses. Table 13 shows that there was an increase in median t<sub>max</sub> across the dose range (from 1 to 3 hours).

Parameter	2.5 mg IC351 (N=16)	5 mg IC351 (N=15)	10 mg IC351 (N=15)	20 mg IC351 (N=16)
AUC (µg*h/L)	900 (27.2)	1888 (27.5)	3647 (34.0)	6809 (24.8)
AUC(0-t <sub>n</sub> ) (µg*h/L)	879 (27.5)	1860 (27.2)	3611 (33.3)	6762 (24.3)
AUC(0-24) (µg*h/L)	596 (23.2)	1175 (19.4)	2265 (19.5)	4221 (16.0)
C <sub>max</sub> (µg/L)	51.6 (16.1)	103 (25.0)	190 (21.7)	322 (21.2)
t <sub>max</sub> (h) <sup>a</sup>	1.01	2.00	2.00	3.00
t <sub>1/2</sub> (h)	16.5 (30.9)	17.3 (33.5)	16.7 (34.4)	16.7 (30.2)
CL/F (L/h)	2.78 (27.2)	2.65 (27.5)	2.74 (34.0)	2.94 (24.8)
V <sub>d</sub> /F (L)	66.0 (20.3)	66.0 (26.0)	66.1 (19.2)	70.9 (17.9)

**Table 13. Geometric Mean (CV%) of pharmacokinetic parameters following oral administration of a single 2.5 mg, 5 mg, 10 mg and 20 mg dose.** Note that this chart was taken from a previously reviewed study.

### 3. H6D-EW-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

##### Summary/Conclusions

This was a double-blind, placebo-controlled, randomized, two-period crossover study 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 N=18 males aged 40-70 years. The primary endpoint was maximal post-baseline drop in standing systolic blood pressure. Note that the study tested the highest recommended oral dose of doxazosin for the treatment of BPH (8 mg QD).

In Study LVFG, a drop in supine and standing blood pressure that persisted until at least 12 hours postdose was observed. Based upon the primary endpoint of maximal post-

baseline drop in standing systolic blood pressure when co-administered with doxazosin, a 20 mg dose of tadalafil could not be declared non-inferior to placebo, as the upper 95% confidence limit (15.5 mmHg) for the mean difference (tadalafil & doxazosin – placebo & doxazosin) was greater than 8 mmHg. The mean difference between the two treatments was 9.81 mmHg.

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, 5/18 subjects (28%) had standing systolic blood pressure less than 85 mmHg following dosing with IC351, compared to 1/18 subject (6%) following dosing with placebo.

66.7% of subjects receiving drug had 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 incidences of severe drug-related adverse events for subjects receiving tadalafil compared to zero incidences for subjects receiving placebo. There were 6 incidences of moderate drug-related adverse events for subjects receiving tadalafil compared to 2 incidences for subjects receiving placebo.

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.

The onset of back pain and myalgia following administration of tadalafil was between 10 and 40 hours after dosing with IC351. For 3 subjects the duration of back pain was long; between approximately 3 to 7 days. The number of subjects experiencing headache, somnolence, fatigue, and vertigo was equivalent after administration of tadalafil and 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.

### **Background**

Patients with benign prostatic hyperplasia (BPH) are often treated with selective alpha 1A-adrenoceptor antagonists such as tamsulosin, which induce a relaxation of prostatic smooth muscles. Alpha 1 antagonists also relax vascular smooth muscles, and have been shown to decrease high blood pressure. Alpha 1 antagonists have a minimal effect, however, on blood pressure of normotensive patients with BPH.

Tadalafil triggers vasodilatation, thus can reduce blood pressure. The rationale for this study was to examine whether concomitant alpha 1 receptor antagonism increased the magnitude of the vascular effects of tadalafil in subjects with BPH. In a previous study performed in healthy subjects (LVAY), no evidence of a significant pharmacodynamic

interaction in terms of the maximum supine systolic and diastolic blood pressure was demonstrated when tamsulosin (0.4 mg once-daily) was co-administered with tadalafil (10 or 20 mg oral doses). The antagonist used in the present study was doxazosin (8 mg once-daily), which is less selective than tamsulosin, and is prescribed for alleviating symptoms in BPH patients as well as reducing blood pressure in hypertensive patients.

## **Objective**

### Primary Objective

To evaluate the effects on blood pressure of coadministration of a single 20 mg tadalafil dose when taken after dosing 8 mg QD doxazosin for 7 days in healthy male subjects.

### Secondary Objective

To assess the safety and tolerability of the drug interaction investigated in the Primary Objective.

## **Design**

- Double-blind, placebo-controlled, randomized, two-period crossover, 10 day washout
- Single dose of 20 mg tadalafil after once-daily dosing (QD) of 8 mg doxazosin for 7 days
- N=18 healthy males; 6 subjects each/age range: 40-50 years, 50-60 years, 60-70 years
- Supine and standing blood pressure measurement times:  
-0.25, 0, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, and 24 hours post tadalafil or placebo dose
- Myalgia tests on Day -1 of treatment period 1, and 48 hours after dosing with tadalafil or placebo in both treatment periods
- Baseline blood pressure: mean of 2 predose measurements

## **Planned Analyses**

- Primary endpoint: maximal post-baseline drop in standing systolic blood pressure
- Secondary endpoints:
  1. Maximal post-baseline drop in supine systolic blood pressure
  2. Maximal post-baseline drop in standing and supine diastolic blood pressure
  3. Maximal post-baseline compensatory increase in standing and supine heart rate
- Data from all subjects were included in the statistical analysis
- The maximal drop in standing and supine systolic and diastolic blood pressure and compensatory increase in standing and supine heart rate were analyzed using a mixed effects model using analysis of variance (ANOVA) techniques of the form:  
$$\text{RESPONSE} = \text{SUBJECT} + \text{PERIOD} + \text{TREATMENT} + \text{RANDOM ERROR}$$
- Non-inferiority for the primary endpoint: upper 95% confidence limit < 8 mmHg

## **Results**

Figure 1 graphically shows the mean change in standing systolic and diastolic blood pressure for 24 hours following tadalafil or placebo administration.

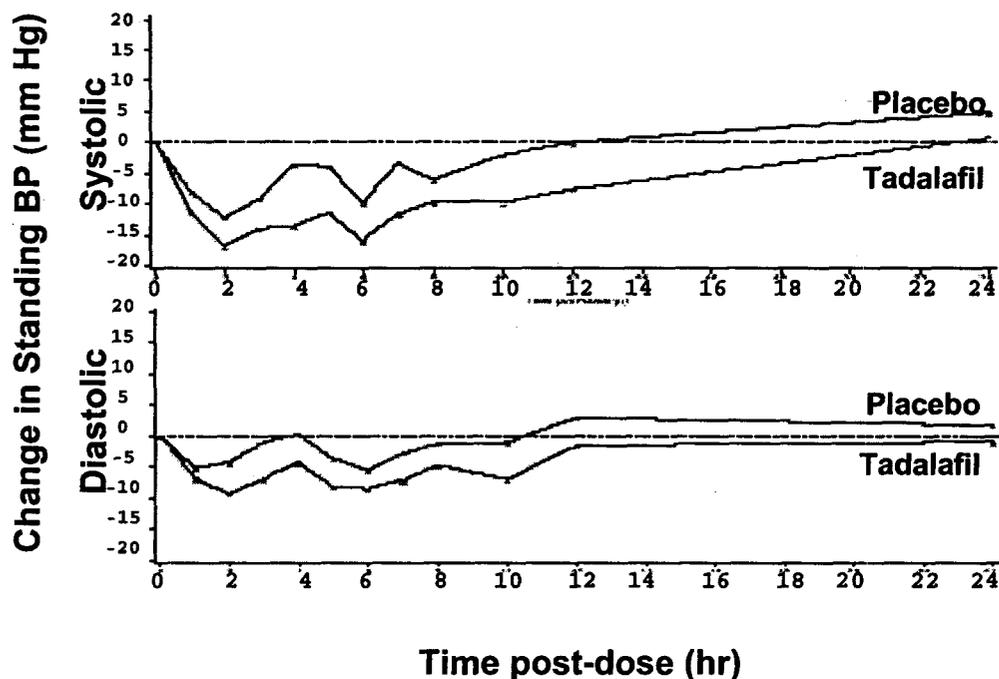


Figure 1. Mean Changes from Baseline in Standing Blood Pressure.

Note:

- Changes greater for tadalafil compared to placebo at all time points
- Mean change in blood pressure on tadalafil returns to baseline at 24 hours versus 12 hours for placebo
- A drop in supine and standing blood pressure persists until at least 12 hours postdose.
- Mean post-baseline drop in standing systolic blood pressure greatest at 2 hours postdose for both treatments, with a secondary drop observed at 6 hours postdose
- Increases in supine and standing heart rate observed

Table 1 shows the results with respect to the primary endpoint: maximal post-baseline drop in standing systolic blood pressure.

Parameter	LS mean		Mean difference <sup>a</sup>	95% confidence limits for the mean difference
	20 mg IC351 & 8 mg q.d. doxazosin	Placebo & 8 mg q.d. doxazosin		
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)

<sup>a</sup> IC351 & doxazosin – placebo & doxazosin

**Table 1. Statistical Analysis of Derived Parameters for Standing Vital Signs**

Note:

- Maximal post-baseline drop in standing systolic blood pressure was greater when tadalafil (IC351) was administered with doxazosin compared to placebo coadministered with doxazosin
- Mean difference (IC351 & doxazosin – placebo & doxazosin) in primary endpoint is 9.81 mmHg
- The mean difference (9.81 mmHg) and upper 95% confidence limit for the mean difference in the primary endpoint (15.5 mmHg) is greater than the pre-defined limit of 8 mmHg for statistical significance
- All three derived parameters of standing vital signs demonstrate statistically significant differences between the treatments.

Table 2 shows the results in terms of clinically significant blood pressure effects:

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)

**Table 2. Number of Subjects [% Subjects] with Potentially Clinically Significant Blood Pressure Effects.**

Note:

For standing systolic blood pressure:

- 5/18 subjects (28% of subjects) had decreases from baseline of greater than 30 mmHg with tadalafil compared to 2/18 subjects (11%) with placebo
- For subjects receiving tadalafil, these decreases were generally in the range of 32 to 41 mmHg; an exception for this was Subject 11 who had a decrease of 71 mmHg (from 121 mmHg at baseline to 50 mmHg). Subject 11 had a potentially clinically significant decrease in standing systolic blood pressure following administration of placebo in Treatment Period 1; a decrease of 31 mmHg, from 131 mmHg at baseline to 100 mmHg at 8 hours post-placebo dose.
- In terms of absolute values, 5/18 subjects (28%) had standing systolic blood pressure less than 85 mmHg following dosing with IC351, compared to 1/18 subject (6%) following dosing with placebo
- Potentially clinically significant blood pressure effects were observed up to 12 hours after dosing with tadalafil

Table 3 shows the results in terms of treatment-emergent adverse events:

Treatment	Subjects [%] with adverse events (all causalities)	Number of adverse events and severity (all causalities)		Subjects [%] with adverse events (drug-related <sup>a</sup> )	Number of adverse events and severity (drug-related <sup>a</sup> )	
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

<sup>a</sup> Adverse events considered to be possibly related to IC351 or placebo

**Table 3. Summary of Treatment-Emergent Adverse Events**

Note:

- There were 2 incidences of severe drug-related adverse events for subjects receiving tadalafil compared to zero incidences for subjects receiving placebo
- There were 6 incidences of moderate drug-related adverse events for subjects receiving tadalafil compared to 2 incidences for subjects receiving placebo
- There were 20 incidences of mild drug-related adverse events for subjects receiving tadalafil compared to 12 incidences for subjects receiving placebo
- 66.7% of subjects receiving drug had a drug-related adverse event compared to 38.9% receiving placebo

Case reports for the two severe drug-related adverse events with tadalafil:

1. Subject 10 reported a severe episode of vertigo approximately 7 hours after dosing with tadalafil; this lasted for approximately 5 days.

Subject 10 had previously experienced a mild episode of vertigo approximately 2 days after dosing with placebo in Treatment Period 1; that episode was considered possibly related to study drug administration and doxazosin.

2. Subject 11 reported a severe episode of dizziness approximately 25 minutes after dosing with tadalafil which lasted for approximately 1 day.

Subject 11 had potentially clinically significant decreases in standing systolic blood pressure 5 and 6 hours after dosing with tadalafil (decreases of 37 and 71 mmHg, respectively, compared to a baseline value of 121 mmHg).

Subject 11 had previously reported a potentially clinically significant decrease in standing systolic blood pressure following dosing with placebo in Treatment Period 1.

Table 4 shows the type and frequency of treatment-emergent drug-related adverse events:

MedDRA term	Number of adverse events [number of subjects with adverse event]	
	20 mg IC351 & 8 mg q.d. doxazosin	Placebo & 8 mg q.d. doxazosin
	(N=18)	(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]	
<b>Total</b>	<b>28 [12]</b>	<b>14 [7]</b>

Source: Section 14.3.4 (Table 2.2)

NOS = Not otherwise specified

**Table 4. Frequency of Treatment-Emergent Study Drug-Related Adverse Events by Type.**

Note:

- 6/18 (33.3%) of subjects receiving tadalafil experienced back pain compared to zero subjects receiving placebo.
- 3/18 (16.7%) of subjects receiving tadalafil experienced dizziness compared to zero subjects receiving placebo.
- 2/18 (11.1%) of subjects receiving tadalafil experienced myalgia compared to zero subjects receiving placebo.
- Onset of back pain and myalgia following administration of tadalafil was between 10 and 40 hours after dosing with IC351. For Subjects 5, 8 and 9, the duration of back pain was long; between approximately 3 to 7 days.
- The number of subjects experiencing headache, somnolence, fatigue, and vertigo was equivalent after administration of tadalafil and placebo.
- 1/18 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.

#### **4. H6D-EW-LVFB:**

**An Investigator- and Subject-Blind, Placebo-Controlled Study to Assess the Electrophysiologic Effect of 100 mg IC351 (Tadalafil) or Placebo on QT Interval with Ibutilide as an Open-Label Positive Control in Healthy Male Subjects**

#### **Summary**

- The sponsor tested the effect of a single 100 mg dose of tadalafil (IC351) on QT interval in a positive- (intravenous ibutilide) and placebo- controlled trial.

- A 100 mg tadalafil dose is 5 times the highest to-be-marketed dose (20 mg). At dose levels greater than 40 mg, tadalafil exposure increases less than proportionally with dose, likely due to decreased absorption.
- The mean tadalafil C<sub>max</sub> and the mean Total IC710 (metabolite) C<sub>max</sub> in this study cover the respective C<sub>max</sub> 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 and/or max tadalafil AUC<sub>0→∞</sub> was not reported for this study. Refer to the “Study Design Evaluation; Relevance of the 100 mg Dose” section of this review for an explanation of how data from a former study of the 100 mg dose suggests that the mean tadalafil AUC in this study
  - (a) covers:
    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
  - (b) 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 sponsor claims that the dose of the positive control used was sensitive to detect a change in QT interval of 8-10 msec. Several aspects of the study design make it difficult to judge whether the positive control was, indeed, sensitive to detect prolongation of such a small duration. Published data suggest that the positive control may cause a mean QTc prolongation as high as 30 msec at the dose tested in this study.
- For an ANOVA model fitting RR as a covariate, the mean change in QTc interval from baseline at 3 hours post-dose observed in the tadalafil and placebo periods was 6.9 and 3.5 ms, respectively. The difference in the mean changes in QTc interval was 3.3 ms 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 QTcI, QTcF, and QTcL was 2.8, 3.5 and 5.0 msec, respectively.
- 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.
- In the ibutilide period, 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. These outlying values were observed in 6.6% and 7.7% of subjects.
- ~10% of the outlying values were >45 msec (but less than 60 msec).

- No individual post-baseline QTc value exceeded 450 msec in the tadalafil and placebo periods.
- One QTcF and two QTcL values greater than 450 msec were observed after the end of ibutilide infusion.
- No subject experienced a QTc change from baseline in the placebo, tadalafil and ibutilide periods greater than 60 msec.
- 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.
- 3 of the adverse events on tadalafil were severe, while zero of the adverse events on placebo or ibutilide were of a severe nature.
- 66 of the adverse events on tadalafil were moderate, while 12 of the adverse events on placebo and 4 on ibutilide 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.
- The sponsor submitted a pharmacokinetic-pharmacodynamic model for the relationship between tadalafil and change in QTc interval. For various reasons, this model cannot be depended upon to make any prediction of QTc change.

## **Objective**

### Primary Objective

To demonstrate that tadalafil has no adverse effect on ventricular repolarization as assessed by QTc when given as a 100 mg single dose.

Evaluate for a statistically significant difference between ibutilide and placebo and/or ibutilide and tadalafil, and for statistical equivalence of tadalafil and placebo.

### Secondary Objective

To assess the safety and tolerability of tadalafil when given as a 100 mg single dose

## **Design**

- A 3-center, randomized, placebo-controlled, crossover study with a positive control
- Healthy males, 18 - 65 years (actually enrolled: 18-53 years)
- 99 subjects entered; 90 subjects completed the study
- 90 subjects received tadalafil and placebo
- 60 subjects received the positive control (intravenous ibutilide)
- Treatments

N=90 100 mg tadalafil (5 x 20 mg tablets; 5 x the highest dose strength)

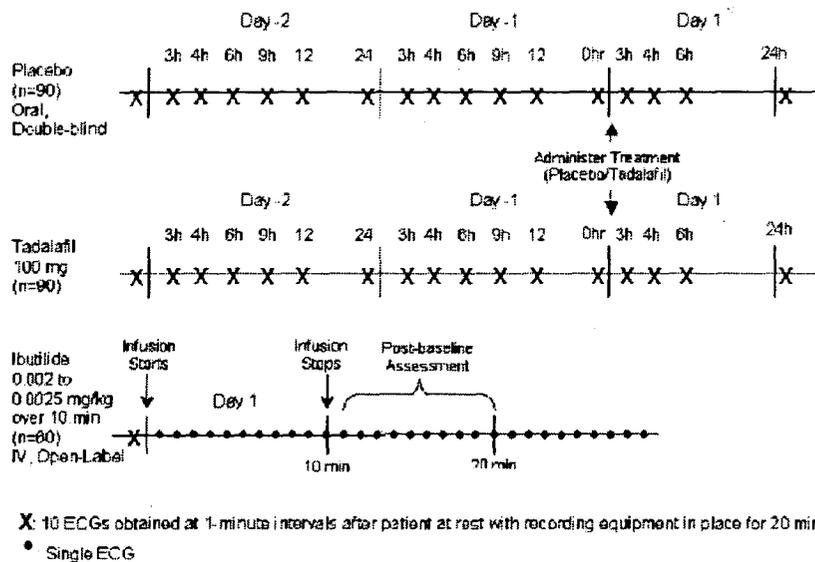
N=60 0.002 mg/kg ibutilide "10-minute" intravenous infusion\*

N=90 Placebo (5 x tablets)

\*Ibutilide infusion for a maximum of 10 minutes. Infusion stopped if a subject had either: (1) two consecutive QTc Bazett readings > 12 msec or (2) a single QTc Bazett reading > 30 msec

- 12 day washout between treatments
- All subjects who received ibutilide infusion received an actual dose of between 0.0005 and 0.0020 mg/kg.
- Tadalafil and placebo were orally administered; ibutilide was intravenously infused
- See Figure 1 for the sampling scheme for Study LVFB. The sponsor measured 10 replicates of QT interval after placebo or tadalafil dosing at 0 (predose), 3, 4, 6, and 24 hours postdose.
- ECG assessments were performed at the time of mean maximum tadalafil plasma concentration (3 or 4 hours post-dose).

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**Figure 1. LVFB Study Design.** For the 0 hour time point, ECGs were taken starting approximately 10 minutes before dosing and finishing at 1 minute before dosing. For all other time points, the set of ten ECGs started approximately 4 minutes before the time point and ended approximately 5 minutes after the time point.

## Planned Analyses

### 1. QT correction for heart rate

#### a) Individual Correction Method (QTcI)

Derived by fitting a linear model to the QT-RR data collected on Day -2 and Day -1 and predose on Day 1 in the tadalafil and placebo periods and predose in the ibutilide period. The estimated slope was used to construct a linear subject-specific QT correction formula.

#### b) Fridericia Correction Method (QTcF)

$$QTcF=QT/RR^{0.333}$$

c) "Lilly" Correction Method (QTcL)

$$QTcL=QT/RR^{0.413}$$

The Lilly population correction is derived from 13,000 ECGs from male and female patients participating in Lilly clinical trials.

## 2. Statistics

### • Primary Statistical Analysis

-Mean change (90% CI) from baseline in QT interval for 100 mg tadalafil versus placebo at peak tadalafil concentration

-Use an ANOVA model having RR interval as a covariate

### • Secondary Statistical Analysis

-Mean change (90% CI) from baseline in QT interval for 100 mg tadalafil versus placebo at peak tadalafil concentration

-Individual (QTcI), Fridericia (QTcF), and Lilly (QTcL) corrected QT values

• Equivalence of the treatments declared if the upper limit of the two-sided 90% CI between placebo and 100 mg tadalafil < 10 msec.

## 3. Details

• Within-subject change from baseline to endpoint in QTc interval in the ibutilide period:  
Start of infusion QTc value – End of infusion QTc value

where,

Start of infusion QTc value = Mean of 10 individual QTc measures prior to infusion

End of infusion QTc value = Mean of QTc intervals measured between 11 and 20 minutes after commencing infusion

• Within-subject change from baseline in QTc interval in the 100 mg tadalafil and placebo periods to a post-baseline time point was defined in several steps:

1. Mean of 10 individual QTc values at each time point computed

2. Change in QTc interval from 0 hours to the selected post-baseline time point (time of peak tadalafil plasma concentration, for example, 3 hours postdose) computed on Days -2, -1 and 1.

3. Changes on Days -2 and -1 (baseline days) were averaged and subtracted from the change on Day 1 (dosing day).

## Results

### (A) Primary Statistical Analysis: Comparison of 100 mg Tadalafil to Placebo

Note the following in Table 1.

• Mean change from baseline in QTc interval for tadalafil: 6.9 msec

• Mean change from baseline in QTc interval for placebo: 3.5 msec

• Difference in the mean changes in QTc interval: 3.3 ms; two-sided 90% CI of (1.7, 5.0).

Treatment	Number of subjects	Change in QTc interval (mean)	Change in QTc interval (standard error)	Difference in change in QTc interval (mean)	Difference in change in QTc interval (90% CI)	P-value
100 mg IC351	90	6.9	0.7	3.3	(1.7, 5.0)	0.0012
Placebo	90	3.5	(0.7)			

**Table 1. Summary of the Mean Change From Baseline in QTc Interval (msec) at Subject's Peak Concentration of tadalafil (IC351).** ANOVA Model with RR Interval as a Covariate, 100 mg Tadalafil versus Placebo. Change in QT and RR intervals was defined as the change from baseline to the time point associated with the peak concentration of tadalafil. The reported two-sided 90% CI and p-value were computed from an ANOVA model for the change in QT interval with the change in RR interval as a covariate and a random subject effect.

**(B) Secondary Statistical Analysis: Comparison of 100 mg Tadalafil to Placebo**

Note the following in Table 2.

- Mean changes in QTcI, QTcF, and QTcL intervals were 2.8, 3.5 and 5.0 msec, respectively.
- The upper limits of the associated two-sided 90% CI were all below 10 msec.

	QTcI interval	QTcF interval	QTcL interval
Change in 100 mg IC351 period			
Mean	6.8	7.1	7.4
(Standard error)	(0.7)	(0.7)	(0.7)
Change in placebo period			
Mean	3.9	3.6	2.4
(Standard error)	(0.7)	(0.7)	(0.7)
Treatment difference			
Mean	2.8	3.5	5.0
(90% CI)	(1.2, 4.4)	(1.9, 5.1)	(3.3, 6.7)

**Table 2. Summary of the Mean Change in QTcI, QTcF, and QTcL Intervals (ms) at Peak Concentration of Tadalafil (100 mg Tadalafil versus Placebo).** The two-sided 90% CI presented were computed from an ANOVA model for the change in QTcI, QTcF, and QTcL intervals with a random subject effect. The change in the corrected intervals was defined as the change from baseline to the time point associated with the peak concentration of tadalafil (IC351).

**Need to Correct for Heart Rate**

Table 3 shows that both tadalafil and placebo affected heart rate in this study at Tmax.

	Heart rate (bpm)	QT interval (ms)
Change in 100 mg IC351 period		
Mean	0.6	6.0
(Standard error)	(0.7)	(1.5)
Change in placebo period		
Mean	-2.5	8.4
(Standard error)	(0.7)	(1.5)
Treatment difference		
Mean	3.1	-2.4
(90% CI)	(1.7, 4.5)	(-5.5, 0.7)

**Table 3. Summary of the Mean Change in Heart Rate and QT interval at Peak Concentration of Tadalafil 100 mg versus Placebo.** The two-sided 90% CI for the treatment difference was computed from an ANOVA model for the change in heart rate and QT interval with a random subject effect.

Note in Table 3:

- A 0.6 beat per minute *increase* in heart rate was observed at peak tadalafil concentration
- A 2.5 beat per minute *decrease* in heart rate was observed following placebo administration.

**Evaluation of Correction Methods**

- Both QTcI and QTcF intervals were virtually independent of heart rate.
- QTcL values were larger at higher heart rates.

**(C) Additional Analyses**

**1. Mean Analysis**

Table 4 shows the change in QTc interval for tadalafil and placebo at 3, 4, 6, and 24 hours postdose.

Time point post-dose (hours)	Treatment	Number of subjects	Change in QTc interval (mean)	Change in QTc interval (standard error)	Difference in Change in QTc interval (mean)	Difference in Change in QTc interval (90% CI)	P-value
3	100 mg IC351	90	7.6	1.7	4.3	(2.6, 6.0)	<0.0001
	Placebo	90	3.3	1.7			
4	100 mg IC351	90	6.5	1.7	3.6	(1.8, 5.2)	0.0004
	Placebo	90	2.9	1.7			
6	100 mg IC351	90	5.0	1.7	4.0	(2.4, 5.6)	<0.0001
	Placebo	90	1.0	1.7			
24	100 mg IC351	90	4.7	1.7	2.3	(0.6, 3.9)	0.0239
	Placebo	90	2.4	1.7			

**Table 4. Summary of the Mean Change in QTc Interval (msec) at 3, 4, 6 and 24 hours postdose.** ANOVA Model with RR Interval as a Covariate, 100 mg Tadalafil versus Placebo. The tadalafil (IC351) values of QTc were greater than those for QTcF and QTcI at all time points.

Note in Table 4:

- Tadalafil causes a greater mean change in QTc than placebo at all time points measured.
- The difference in the mean QTc change between tadalafil and placebo is approximately 4 msec at 3, 4, and 6 hours postdose. The difference decreases to 2.3 msec at 24 hours postdose.
- The difference between tadalafil and placebo is statistically significant at all time points measured.

**Ibutilide versus Tadalafil**

Table 5 summarizes QTc interval changes in the tadalafil and ibutilide periods. The mean treatment difference in QTc interval change from baseline equaled 6.8 msec with the two-sided 90% CI of (5.0,8.7). Note the difference between the mean change in QTc from baseline for tadalafil reported here (5.9 msec) and reported in Table 1 (6.9 msec). The discrepancy is explained by a difference in the patient sample. Table 1 is based on data in 90 subjects while Table 5 is based on data in 62 subjects. Recall that ibutilide was only dosed to a subset of the study population.

Treatment	Number of subjects	Change in QTc interval (mean)	Change in QTc interval (standard error)	Difference in change in QTc interval (mean)	Difference in change in QTc interval (90% CI)	P-value
Ibutilide	62	12.7	0.8	6.8	(5.0, 8.7)	<0.0001
100 mg IC351	62	5.9	0.8			

**Table 5. Summary of the Mean Change in QTc Interval (ms) at Peak Concentration of tadalafil (IC351).** ANOVA Model with RR Interval as a Covariate. The change in QT and RR intervals in the IC351 (tadalafil) and placebo periods was defined as the change from baseline to the time point associated with the peak concentration of tadalafil. The change in QT and RR intervals in the ibutilide period was defined as the change from pre-infusion to the end of infusion. The p-value and two-sided 90% CI shown in the table were computed from an ANOVA model for the change in QT interval with the change in RR interval as a covariate and a random subject effect.

### Ibutilide versus Placebo

Table 6 summarizes QTc interval changes in the placebo and ibutilide periods. The difference in the mean QTc interval change between the two periods was 9.6 msec. Note the difference between the mean change in QTc from baseline for placebo reported here (3.0 msec) and reported in Table 1 (3.5 msec). The discrepancy is explained by a difference in the patient sample. Table 1 is based on data in 90 subjects while Table 6 is based on data in 61 subjects. Recall that ibutilide was only dosed to a subset of the study population.

Treatment	Number of subjects	Change in QTc interval (mean)	Change in QTc interval (standard error)	Difference in change in QTc interval (mean)	Difference in change in QTc interval (90% CI)	P-value
Ibutilide	61	12.7	0.8	9.6	(7.6, 11.6)	<0.0001
Placebo	61	3.0	0.9			

**Table 6. Summary of the Mean Change in QTc Interval (ms) at Peak Concentration of tadalafil (IC351).** ANOVA Model with RR Interval as a Covariate, Ibutilide versus placebo.

## 2. Outlier Analysis

Analysis of 8,011 individual ECG QTc measurements was performed based upon a comparison of the percentage of subjects and the percentage of observations of QTc interval (corrected for heart rate using the individual, Fridericia and Lilly formulas):

- (a) greater than 450 and 500 msec at the baseline and post-baseline assessments
- (b) increased from baseline by more than 30, 60, and 75 msec.

The analysis for each subject was based on up to 40 post-baseline ECG recordings in the tadalafil and placebo periods and up to 10 post-infusion ECG recordings in the ibutilide period.

Note that:

- No individual post-baseline QTc value exceeded 450 msec in the tadalafil and placebo periods.
- One QTcF and two QTcL values greater than 450 msec were observed after the end of ibutilide infusion.

- No subject experienced a QTc change from baseline in the placebo, tadalafil and ibutilide periods greater than 60 msec.

Table 7 and Table 8 report the values with respect to the 30 msec outlier cutoff.

	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)

**Table 7. Summary of Outlier Changes in QTcI, QTcF, and QTcL Values.** 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)

**Table 8. Number (Percent) of Subjects with at Least One Change in QTcI, QTcF or QTcL >30 msec.**

Note that:

- 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. In contrast, 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. These outlying values were observed in 6.6% and 7.7% of subjects.
- ~10% of the outlying values were >45 msec (but less than 60 msec).

The sponsor submitted an outlier analysis performed on the mean of each subjects' 10 individual ECG QTc values at Tmax. Given that it involves averaging QTc values, it is not a valid outlier analysis in the usual sense of the word. However, it serves to indicate any extreme outliers since any subject whose average value exceeds a value considered an outlying value for a single measurement is exceptionally outlying.

According to this analysis, no subject was observed to have a mean change from baseline of greater than 60 msec at Tmax. No individual post-baseline mean QTc values exceeding 450 msec were detected in the tadalafil and placebo periods, whereas one and three individual mean QTc values were greater than 450 msec were observed after the

end of ibutilide infusion using the Fridericia and Lilly correction formulas, respectively. Table 9 shows the percentage of subjects who experienced a mean change in QTc greater than 30 msec at Tmax. Note that 1 subject had a mean QTcF and QTcL greater than 30msec at Tmax.

	100 mg IC351 (N=90) n(%)	Placebo (N=90) n(%)	P-value
Change in QTcI interval >30 ms	0(0.0)	0(0.0)	-
Change in QTcF interval >30 ms	1(1.1)	0(0.0)	1.000
Change in QTcL interval >30 ms	1(1.1)	0(0.0)	1.000

**Table 9. Percent of subjects with a mean change in QTcI, QTcF, and QTcL intervals from baseline to the time point associated with the peak concentration of tadalafil (IC351) in the IC351 and placebo periods.** Given that this analysis involves averaging QTc values, it is not a valid outlier analysis in the customary sense of the word. However, it serves to indicate any exceptional outliers since any subject whose average value exceeds a value considered an outlying value is likely cause for concern.

### 3. Concentration-Response Analysis

The sponsor submitted Figure 2—a plot and regression line fit to the data on the change in QTcI from baseline as a function of tadalafil plasma concentration at 3, 4, 6, and 24 hours postdose. For reference, lines depicting the maximum plasma concentration during daily dosing of 20 mg tadalafil (880 µg/L) and following a single 20 mg dose of tadalafil with maximum 3A4 inhibition (1161 µg/L) are displayed on the plots. In total, 108 (29.1%) of the plasma samples in this study exceeded 880 µg/L and 25 (6.7%) exceeded 1161 µg/L.

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 are few data points at concentrations greater than 1161 µg/L, each of these extreme points likely exert great leverage. Second, the sponsor provided no information on the goodness of fit of the model. It would be especially interesting to see how well the population fit agrees with the models for individual datasets. Finally, response was smaller with respect to QTcI than any other correction method used (see Table 1 and Table 2).

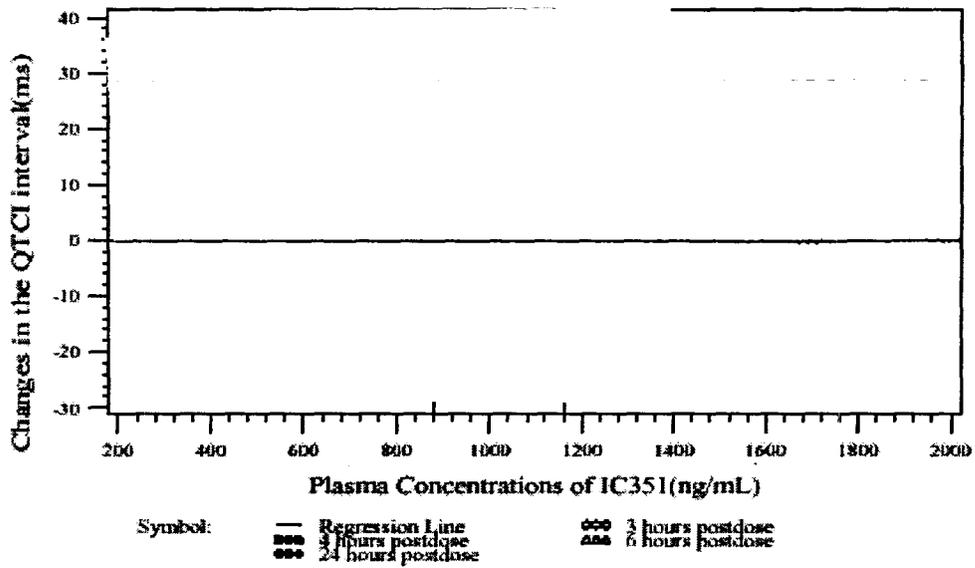


Figure 2. Scatter Plot of Changes in QTcI Interval (ms) versus Plasma Concentration of Tadalafil (IC351). Data from all time points used.

Figure 3 is analogous to Figure 2, except that the change in QTcI is plotted as a function of Total IC710 concentration.

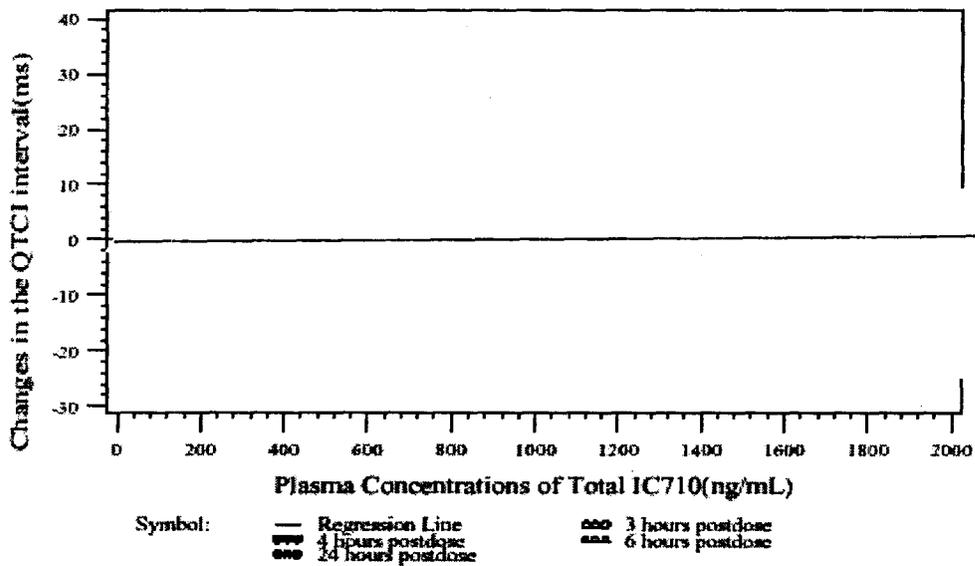


Figure 3. Scatter Plot of Changes in QTcI Interval (msec) versus Plasma Concentration of Total IC710.

The sponsor claims that the observed negative trend in changes in QTc interval indicates that higher concentrations of total IC710 do not cause increases in the QTcI. The same critique of Figure 2 applies to this claim.

## Safety and Tolerability

Table 10 and Table 11 summarize the treatment-emergent adverse events observed in this study.

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

Source: Section 14.3.4 (Tables 1.1 and 1.2)

N = Number of subjects studied

<sup>a</sup> Relationship of possible or probable following administration of IC351 or placebo; relationship of related to ibutilide following administration of ibutilide

**Table 10. Frequency of Treatment-Emergent Adverse Events by Severity.**

Note that:

- 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.
- 3 of the adverse events on tadalafil were severe, while zero of the adverse events on placebo or ibutilide were of a severe nature.
- 66 of the adverse events on tadalafil were moderate, while 12 of the adverse events on placebo and 4 on ibutilide were of a moderate nature.

Table 10 shows:

- 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.

- The adverse events occurring more frequently after tadalafil versus placebo or ibutilide dosing include flushing, pain in limb, arthralgia, nausea, spontaneous penile erection, headache, nasal congestion, eye pain, and dyspepsia.

MedDRA term	Number of adverse events [number of subjects with adverse event]		
	100 mg IC351 (N=92)	Placebo (N=91)	0.002 mg/kg ibutilide <sup>a</sup> (N=67)
Headache NOS	101 [71]	16 [11]	2 [2]
Back pain	24 [21]	2 [2]	1 [1]
Nasal congestion	21 [20]		1 [1]
Myalgia	20 [18]	1 [1]	
Dizziness	15 [10]	3 [2]	3 [3]
Flushing	16 [15]	2 [2]	
Pain in limb	13 [12]	1 [1]	2 [1]
Arthralgia	13 [9]	2 [2]	
Nausea	9 [8]	1 [1]	2 [2]
Spontaneous penile erection	9 [9]	1 [1]	
Eye pain	8 [5]		
Dyspepsia	6 [4]	1 [1]	
Pharyngitis	4 [4]	1 [1]	1 [1]
Diarrhoea NOS	2 [2]	1 [1]	2 [2]
Paraesthesia	1 [1]	1 [1]	3 [2]
Toothache		4 [3]	1 [1]
Pain NOS	4 [3]		
Nasopharyngitis	1 [1]		3 [3]
Palpitations	1 [1]		3 [3]
Rhinorrhoea	2 [2]		2 [2]
Feeling hot	2 [2]	1 [1]	1 [1]
Dry mouth	3 [3]		
Somnolence	3 [2]		
Fatigue	2 [2]	1 [1]	
Neck pain	2 [2]		1 [1]
Herpes simplex			2 [2]
Influenza like illness	2 [2]		
Muscle cramps	2 [2]		

Source: Section 14.3.4 (Table 2.2)

N= Number of subjects

<sup>a</sup> Adverse events related to ibutilide

**Table 10. Frequency of Treatment-Emergent Adverse Events by Type.**

## Study Design Evaluation

### 1. Relevance of the 100 mg dose

Figure 4 shows the mean tadalafil and metabolite concentrations up to 24 hours after dosing 100 mg tadalafil. Figure 5 shows the corresponding individual plots of data for tadalafil and Figure 6 shows the corresponding plot of Total IC710.

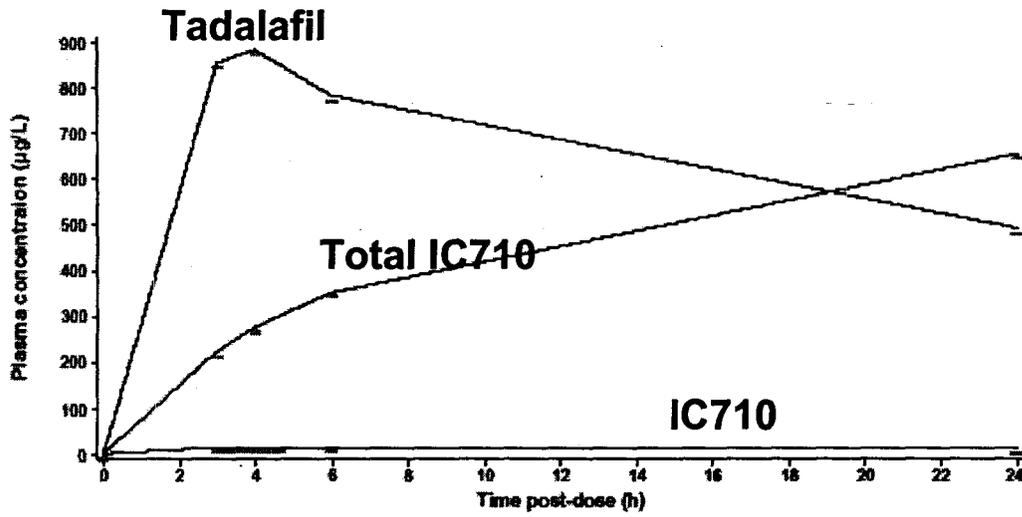


Figure 4. Arithmetic mean plasma concentration-time profiles of tadalafil (N=92), total IC710 (N=92), and IC710 (N=92) after a single oral dose of 100 mg tadalafil. Mean tadalafil C<sub>max</sub> is 883 µg/L and mean Total IC710 C<sub>max</sub> is 653 µg/L (last measurement taken).

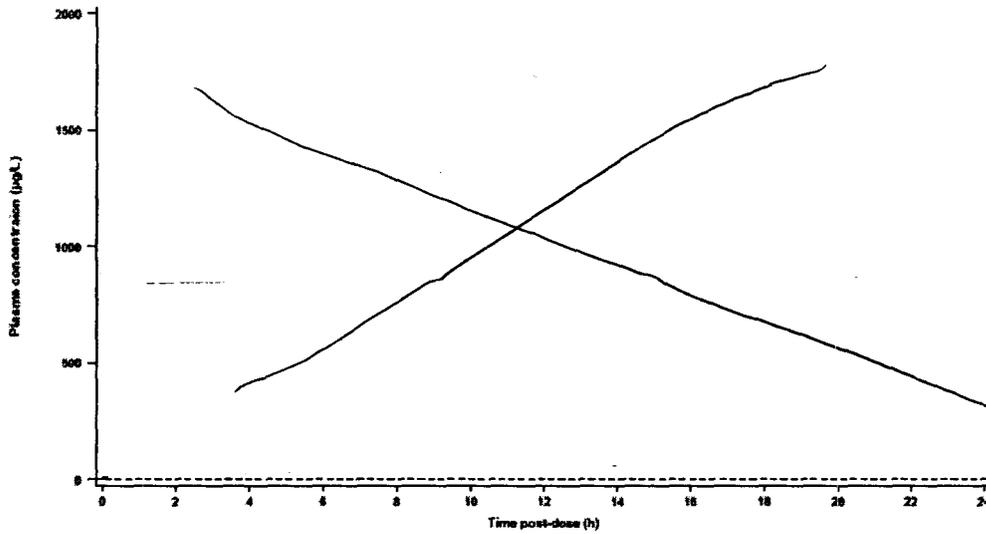
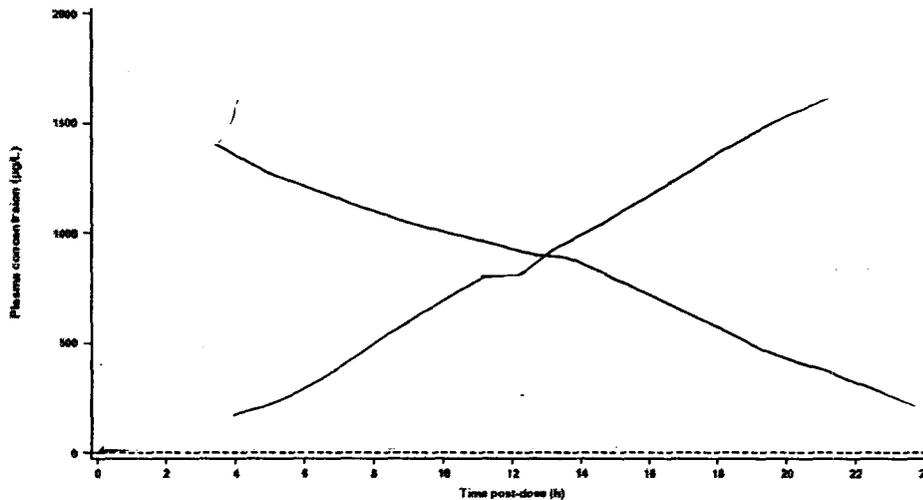


Figure 5. Individual Changes in Tadalafil Concentration with Time for the 100 mg Tadalafil Dose. Maximum C<sub>max</sub> is 1973 µg/L..



**Figure 6. Individual Changes in Total IC710 Concentration with Time for the 100 mg Tadalafil Dose.** Mean C<sub>max</sub> (at 24 hours—the end of the collection period) is 653 µg/L and maximum C<sub>max</sub> is approximately 1600 µg/L.

No formal pharmacokinetic analyses of these data was performed. Individual plasma concentrations were generally similar for all subjects at 3 and 4 hours postdose (range: \_\_\_\_\_ respectively). More subjects reached T<sub>max</sub> at 3 hours postdose. Plasma concentrations of total IC710 increased steadily following administration of 100 mg tadalafil with a maximum arithmetic mean plasma concentration (653 µg/L) observed at 24 hours postdose—the last blood sampling time point.

The sponsor provided Table 11 to show how the concentrations of tadalafil and metabolites in this study cover concentrations achieved under various scenarios that alter drug exposure.

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Study	Treatment	Time postdose	Analyte	Plasma concentration ( $\mu\text{g/L}$ )	
				Arithmetic mean	Maximum <sup>a</sup>
LVFB	100 mg IC351 SD	4 hours	IC351	883	1940
			Total IC710	653 <sup>b</sup>	1659 <sup>b</sup>
			IC710	15.2	53.2 <sup>c</sup>
LVDK (Steady state)	20 mg IC351 MD	Day 5, 2 hours <sup>d</sup>	IC351	515	880
			Total IC710	473	702 <sup>e</sup>
			IC710	9.44	23.4 <sup>f</sup>
LVDT (Renally impaired)	20 mg IC351 SD	2 hours	IC351	639	825
			Total IC710	71.9 <sup>g</sup>	179 <sup>g</sup>
			IC710	4.36	8.36 <sup>g</sup>
LVEV (CYP3A4 inhibition)	20 mg IC351 SD	2 hours	IC351	526 <sup>g</sup>	973
			Total IC710	167 <sup>b</sup>	314 <sup>b</sup>
			IC710	4.70 <sup>g</sup>	8.46 <sup>c</sup>
	20 mg IC351 SD & 200 mg bid ritonavir	4 hours	IC351	533	941
			Total IC710	29.4 <sup>b</sup>	55.2 <sup>b</sup>
			IC710	ND	ND
	20 mg IC351 SD & 400 mg od ketoconazole	4 hours	IC351	691	1161 <sup>e</sup>
Total IC710			58.2 <sup>b</sup>	86.6 <sup>b</sup>	
IC710			ND	ND	

**Table 11. Comparison of Arithmetic Mean and Maximum Plasma Tadalafil Concentrations Following Administration of 20 and 100 mg Tadalafil.** Note that: SD = Single dose, MD = Multiple dose (for 10 days), ND = Not determined, bid = twice daily, od = Once daily, a = Individual maximum concentration at that time point, b=Maximum concentration observed at 24 hours postdose, c=Maximum concentration observed at 3 hours postdose, d=Steady state achieved by Day 5, e=Maximum concentration observed on Day 7 at 3 hours postdose, f= Maximum concentration observed on Day 10 at 2 hours postdose, and g=Maximum concentration observed at 4 hours postdose.

This table suggests that the mean and maximum C<sub>max</sub> values of tadalafil and metabolites achieved in this study cover the values expected: (a) 2 hours after dosing 20 mg tadalafil at steady state, (b) 2 hours after dosing 20 mg tadalafil to renally impaired subjects, and (c) 4 hours after dosing 20 mg tadalafil with either of the potent CYP 3A4 inhibitors ritonavir (200 mg bid) or ketoconazole (400 mg qd).

The mean and/or max AUC<sub>0-∞</sub> for the 100 mg dose of tadalafil was not reported in this study, as the sponsor conducted no formal PK analysis. AUC for a 100 mg tadalafil dose in this study can be estimated based on the results of a former study, Study LVBH, which investigated a single 100 mg tadalafil dose in 6 elderly men. In Study LVBH, the mean and range of AUC was \_\_\_\_\_ respectively. Given that AUC in the elderly is 25% higher relative to healthy subjects, an estimate of mean AUC is 20000  $\mu\text{g}\cdot\text{h/L}$  with a range of \_\_\_\_\_

In a formerly reviewed studies:

- The AUC following once-daily administration of a 20 mg dose for 5 days (steady state) was reported as 7692 micrograms $\cdot\text{h/L}$  (31.1% CV).
- When 20 mg tadalafil was dosed in subjects with end-stage renal failure receiving hemodialysis, mean tadalafil AUC was 18090  $\mu\text{g}\cdot\text{h/L}$  (CV=38.8%).

- When 10 mg tadalafil was dosed in subjects with moderate and mild renal impairment, mean tadalafil AUC was 4911  $\mu\text{g}\cdot\text{hr}/\text{L}$  (CV=50.1%).
- The mean  $\text{AUC}_{0\rightarrow\infty}$  observed during an interaction study of 20 mg tadalafil and 400 mg ketoconazole (Study LVEV) was 53,524  $\mu\text{g}\cdot\text{h}/\text{L}$  (CV = 49.2%).
- The mean tadalafil  $\text{AUC}_{0\rightarrow\infty}$  and observed during an interaction study of 20 mg tadalafil and 200 mg BID ritonavir (Study LVEV) was 33,033  $\mu\text{g}\cdot\text{h}/\text{L}$  (CV = 40.3%)

Based on this estimate, tadalafil's AUC for the 100 mg dose is expected to cover the value expected at steady state (7692 micrograms\*h/L) and mean AUC when 20 mg tadalafil is dosed in subjects with end-stage renal failure (18090  $\mu\text{g}\cdot\text{h}/\text{L}$ ) and renal impairment.

The AUC for the 100 mg tadalafil dose in this study, based on the results of Study LVBH does not cover the mean nor the range of AUCs expected for the interaction with ritonavir or ketoconazole.

## 2. Validity of the positive control

The purpose of the positive control in this study is to demonstrate that the study is sensitive enough to detect a change in QT interval on the order of 10msec. The reason being that in the event no significant change in QT interval is detected for the test compound, there is evidence to show that the study was powered to find a change of the relevant magnitude.

Therapeutic doses of ibutilide are associated with much larger 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. An extensive literature search revealed only one published study with a dose approximating that used by the sponsor.<sup>1</sup> This publication was referenced by the sponsor in justifying the ibutilide dose used.

The sponsor ran a dose-finding study and claims that a 0.0025 mg/kg IV dose of ibutilide infused for 10 minutes causes an average change of 10 msec. However, a published report shows that a 0.003 mg/kg IV dose of ibutilide infused for 10 minutes causes an average of ~30 msec change in QT interval.<sup>1,2</sup>

Rodriguez, et. al. investigated the response to a 10 minute infusion of 0.003 mg/kg ibutilide infusions in 38 males and 20 females aged 21 to 40 years. The mean change in Bazett's corrected QTc (QTcB) as a function of time was as follows.

Time (minutes)	Female $\Delta\text{QT}_{\text{cB}}$ (msec)	Male $\Delta\text{QT}_{\text{cB}}$ (msec)	Female SEM	Male SEM
0	0	0	0.00	0.00
5	22	11	3.18	2.37
10	44	32	3.48	2.39
15	52	37	3.85	2.84
20	43	36	3.09	2.59

30	36	30	4.40	2.87
40	33	26	3.25	2.48
50	26	14	2.16	2.83
60	27	18	3.16	2.53
90	24	7	3.90	3.56
120	18	8	3.65	4.71

One possibility, 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. Another possibility is that the sponsor's infusion scheme assured that the positive control caused 10 msec of change. (The sponsor's protocol required that the infusion be stopped if there were two consecutive readings of QTcB > 12 msec in a subject.) A third possibility is that the 0.0025 mg/kg dose causes 30 msec change but the study was not designed to find a change of that magnitude.

The sponsor's dose-finding study for ibutilide is difficult for two reasons. First, the infusion was stopped if two consecutive measured values of QTcB were greater than 12 msec or one measure was greater than 30 msec. Since QTcB is known to overcorrect for heart rate, the infusion was stopped at values of QTcI, QTcF, and QTcL, likely smaller than 12 msec. Second, QT measurement is noisy. Thus, two consecutive measures of QTcB > 12 msec or one measure > 30 msec is not necessarily indicative of a clinically relevant change in QTc.

To the extent that there is a direct exposure-response relationship for ibutilide, the sponsor's approach is more valid. Note that the maximum change in QTc observed occurred 5 minutes after the termination of infusion (at 15 minutes) for both males and females in Rodriguez' study. Most likely, the "true" change in QTc caused by the positive control used in this study is greater than 10 msec, but much less than 30 msec.

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

## **Background**

### **Positive Control**

- Ibutilide fumarate injection is an antiarrhythmic agent with predominantly class III cardiac action potential prolongation, i.e. it increases both atrial and ventricular refractoriness *in vivo*.
- Oral formulation of ibutilide exists but the sponsor justified the use of the intravenous formulation as allowing rapid termination of effects and titration of effects.
- Voltage clamp studies indicate that Ibutilide, at nanomolar concentrations, delays repolarization by activation of a slow, inward current (predominantly sodium), rather than by blocking outward potassium currents, which is the mechanism by which other class III antiarrhythmics act. These effects lead to prolongation of atrial and ventricular

action potential duration and refractoriness, the predominant electrophysiologic properties of Ibutilide in humans that are thought to be the basis for its antiarrhythmic effect.

- Ibutilide produces no clinically significant effect on QRS duration at intravenous doses up to 0.03 mg/kg administered over a 10-minute period. Although there is no established relationship between plasma concentration and antiarrhythmic effect, Ibutilide produces dose-related prolongation of the QT interval, which is thought to be associated with its antiarrhythmic activity. In a study in healthy volunteers, intravenous infusions of Ibutilide resulted in prolongation of the QT interval that was directly correlated with ibutilide plasma concentration during and after 10-minute and 8-hour infusions. A steep ibutilide concentration/response (QT prolongation) relationship was shown. The maximum effect was a function of both the dose of Ibutilide and the infusion rate.
- After intravenous infusion, ibutilide plasma concentrations rapidly decrease in a multiexponential fashion. The pharmacokinetics of ibutilide are highly variable among subjects. Ibutilide has a high systemic plasma clearance that approximates liver blood flow (about 29 mL/min/kg), a large steady-state volume of distribution (about 11 L/kg) in healthy volunteers, and minimal (about 40%) protein binding. Ibutilide is also cleared rapidly and highly distributed in patients being treated for atrial flutter or atrial fibrillation. The elimination half-life averages about 6 hours (range from 2 to 12 hours). The pharmacokinetics of ibutilide are linear with respect to the dose of CORVERT over the dose range of 0.01 mg/kg to 0.10 mg/kg.

#### Pharmacokinetics

- Tadalafil is a low hepatic clearance drug with a geometric mean terminal t<sub>1/2</sub> of 17.5 hours.
- The accumulation index for once-daily administration of a 20 mg dose (at 5 and 10 days) is 1.6.
- In a formerly reviewed study, the C<sub>max</sub> (at steady state) following once-daily administration of a 20 mg dose for 5 days was reported as 514 micrograms/L (26.8% CV). The mean C<sub>max</sub> in this study (883 µg/L) covers the C<sub>max</sub> value expected at steady state.
- The mean C<sub>max</sub> observed during an interaction study of 20 mg tadalafil and 400 mg ketoconazole (Study LVEV) was 669.731 µg/L (CV = 29.9%). The mean C<sub>max</sub> in this study (883 µg/L) covers the C<sub>max</sub> value expected for this interaction.
- The mean tadalafil C<sub>max</sub> observed during an interaction study of 20 mg tadalafil and 200 mg BID ritonavir (Study LVEV) was 533.887 µg/L (CV = 25.3%). The mean tadalafil C<sub>max</sub> in this study (883 µg/L) covers the C<sub>max</sub> value expected for this interaction.
- When 20 mg tadalafil was dosed in subjects with end-stage renal failure receiving hemodialysis, mean tadalafil C<sub>max</sub> was 621 µg/L (CV=26.6%). The C<sub>max</sub> in this study covers this scenario.
- When 10 mg tadalafil was dosed in subjects with moderate and mild renal impairment, mean tadalafil C<sub>max</sub> was 220 µg/L (CV=22.2%) and 217 (CV=21.0%), respectively. The C<sub>max</sub> in this study covers this scenario.
- The mean and max Total IC710 C<sub>max</sub> for the 100 mg dose of tadalafil in this study were 653 and 1600 µg/L, respectively.

- Arithmetic mean and maximum individual plasma concentrations of total IC710 and IC710 achieved following a single dose of 100 mg tadalafil were greater than those achieved at steady state following once daily dosing with 20 mg tadalafil alone.
- Arithmetic mean and maximum individual plasma concentrations of total IC710 and IC710 achieved following a single dose of 100 mg tadalafil were greater than those achieved after dosing 20 mg tadalafil with 200 mg BID ritonavir or with 400 mg QD ketoconazole.
- Mean IC710  $AUC_{0 \rightarrow t=144 \text{ hrs}}$  in subjects with ESRF receiving hemodialysis after a 20 mg tadalafil dose was 32,229  $\mu\text{g}\cdot\text{h}/\text{L}$  (24.5 = CV%) and mean  $C_{\text{max}}$  was 300  $\mu\text{g}/\text{L}$  (26.1 = CV%). The mean Total IC710  $C_{\text{max}}$  in this study (653  $\mu\text{g}/\text{L}$ ) covers the  $C_{\text{max}}$  value.
- Mean IC710  $C_{\text{max}}$  in subjects with moderate and mild renal impairment after a 10 mg tadalafil dose was 142  $\mu\text{g}/\text{L}$  (26.3=CV%) and 113  $\mu\text{g}/\text{L}$  (43.7=CV%), respectively. The mean IC710  $C_{\text{max}}$  in this study (300  $\mu\text{g}/\text{L}$ ; CV%=26.1) covers this level.
- The mean and maximum change in AUC observed for a drug interaction with a CYP 3A4 inhibitor (Study LVEV) was with 400 mg QT ketoconazole. In this case,  $AUC_{0 \rightarrow \infty}$  increased 4.1-fold on average and the most extreme change was 5.9-fold. In addition,  $C_{\text{max}}$  increased 1.2-fold on average and the most extreme change was 1.9-fold.
- The mean and/or max  $AUC_{0 \rightarrow \infty}$  for the 100 mg dose of tadalafil was not reported for this study, as the sponsor conducted no formal PK analysis. AUC for the 100 mg tadalafil dose in this study can be estimated based on the results of a former study, Study LVBH, which investigated a single 100 mg tadalafil dose in 6 elderly men. In Study LVBH, the mean and range of AUC was \_\_\_\_\_ respectively. Given that AUC in the elderly is 25% higher relative to healthy subjects, an estimate of mean AUC is 20000  $\mu\text{g}\cdot\text{h}/\text{L}$  with a range of \_\_\_\_\_
- The mean and max tadalafil  $C_{\text{max}}$  for the 100 mg dose of tadalafil in this study were 883 and 1973  $\mu\text{g}/\text{L}$ , respectively.
- In a former study (LVBH) where 100 mg tadalafil was administered once daily for seven consecutive days to 6 elderly men, on day 7, mean  $C_{\text{max}}$  was 723  $\mu\text{g}/\text{L}$ , range: \_\_\_\_\_ mean  $T_{\text{max}}$  was 3 hours and ranged from 2-4 hours, and mean  $AUC_{0 \rightarrow 24}$  was 12530  $\mu\text{g}\cdot\text{h}/\text{L}$ , range: \_\_\_\_\_
- In a former study (LVBH) when a *single* 100 mg tadalafil dose was administered to 6 elderly men, mean  $C_{\text{max}}$  was 576  $\mu\text{g}/\text{L}$  and ranged from \_\_\_\_\_ . Mean  $t_{\text{max}}$  was 8.7 hours and ranged from 2-24 hours. Mean AUC was 24708  $\mu\text{g}\cdot\text{h}/\text{L}$  and ranged from \_\_\_\_\_
- The AUC at steady state (following once-daily administration of a 20 mg dose for 5 days) was 7692 micrograms $\cdot\text{h}/\text{L}$  (31.1% CV). The mean AUC in this study covers this scenario.
- When 20 mg tadalafil was dosed in subjects with end-stage renal failure receiving hemodialysis, mean tadalafil AUC was 18090  $\mu\text{g}\cdot\text{h}/\text{L}$  (CV=38.8%). The mean AUC in this study covers this scenario.
- When 10 mg tadalafil was dosed in subjects with moderate and mild renal impairment, mean tadalafil AUC was 4911  $\mu\text{g}\cdot\text{hr}/\text{L}$  (CV=50.1%) and 6280  $\mu\text{g}\cdot\text{hr}/\text{L}$  (CV=46.1%); respectively. The tadalafil AUC predicted in this study covers this scenario.
- The mean  $AUC_{0 \rightarrow \infty}$  observed during an interaction study of 20 mg tadalafil and 400 mg ketoconazole (Study LVEV) was 53,524  $\mu\text{g}\cdot\text{h}/\text{L}$  (CV = 49.2%). The AUC for the 100 mg

tadalafil dose in this study, based on the results of Study LVBH (mean: 24708  $\mu\text{g}\cdot\text{h}/\text{L}$ ; range: \_\_\_\_\_ ) does not cover the mean nor the range of AUCs expected for this interaction.

- The mean tadalafil  $\text{AUC}_{0\rightarrow\infty}$  observed during an interaction study of 20 mg tadalafil and 200 mg BID ritonavir (Study LVEV) was 33,033  $\mu\text{g}\cdot\text{h}/\text{L}$  (CV = 40.3%). The tadalafil AUC for the 100 mg tadalafil dose in this study, based on the results of Study LVBH (mean: 24708  $\mu\text{g}\cdot\text{h}/\text{L}$ ; range: \_\_\_\_\_ ) does not cover the mean AUC expected for this interaction. However, it does fall within the range of AUCs observed for this interaction.

### 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. 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 (PILOT STUDY for LVFB)

#### Objective

- Determine an infusion rate and dose for ibutilide that is likely to result in an increase in QTc interval of approximately 8 to 10 msec at the end of a 10-minute intravenous infusion. Ibutilide at this dose and infusion rate will be used in the main study (LVFB) as a positive control.

#### Design

- Multi-center, randomized, open-label pilot study
- Healthy males, 18-65 years
- Seventeen subjects entered
- 16 subjects completed, 20-63 years, all but 1 Caucasian (1 African American)
  - 12 subjects received 2 ibutilide doses, 1 placebo dose
  - 4 subjects received 3 ibutilide doses
  - 1 subject received 2 ibutilide doses
- Different subjects than in main study
- Dosing regimen for each subject:
  - Day 1 or 2 or 3      One 10-minute infusion of ibutilide
  - Day 1 or 2 or 3      One 10-minute infusion of ibutilide
  - Day 1 or 2 or 3      One 10-minute infusion of placebo
- Measurement of ECG at 1 minute intervals for each subject:
  - 20 minutes of predose measurement (start ~30 minutes before dosing)
  - During ibutilide infusion (10 minute infusion)
  - 20 minutes following ibutilide infusion
- Decision to increase/decrease dose of ibutilide on second dosing occasion depended on change in QTc interval observed with previous ibutilide dose

- Ibutilide infusion was terminated if the QTc interval increased by more than 12 msec on two consecutive readings (at 1-minute intervals)
- If a single 30 msec change from baseline determined by machine reading was observed, the recording was reviewed by a study investigator to ensure that the change was not artefactual before terminating infusion
- Dosing at approximately the same time each day
- PDR reports that the mean t1/2 for ibutilide is 6 hours but ranges from 2-12 hours; washout may not have been ensured for the following subjects:

- +Placebo dosed after 2 days of ibutilide dosing for all 6 subjects in Center 1
- +Placebo dosed after 1 day of ibutilide dosing for Subject 7 in Center 2

Note that placebo was dosed before 2 days of ibutilide dosing for 5 subjects in Center 2 and for 1 day before ibutilide dosing for 1 subject in Center 2.

### Methods

- 12-lead QTc ECGs measured by machine using Bazett's heart rate correction
- ECGs sent to a central ECG vendor for central overread
- Ibutilide: intravenous infusion (0.0009 to 0.0025 mg/kg) for 10 minutes
- Placebo (0.9% sodium chloride solution): intravenous infusion for 10 minutes
- Ibutilide (Corvert ®) was supplied by Lilly ICOS LLC

### Data Analysis

- Maximum change in QTc interval over the 1-hour period following the end of ibutilide infusion:

$$\max_{\text{IBUTILIDE}} \Delta \text{QTc}_{\text{IBUTILIDE}}^{\text{TIMEpost-ibutilide: } x=0 \text{ hr} : x=1 \text{ hr}} | \text{subject, dose} = \text{maximum}(\text{QTc}_{\text{IBUTILIDE}}^{\text{TIMEpost-ibutilide}=xi} | \text{subject, dose}) - \text{mean}(\text{QTc}_{\text{IBUT}}^{\text{TIMEpost-ibutilide: } x=-0.5 \text{ hr} : x=0 \text{ hr}} | \text{subject, dose})$$

- Maximum change in QTc interval over the 1-hour period following the end of placebo infusion:

$$\max_{\text{PLACEBO}} \Delta \text{QTc}_{\text{PLACEBO}}^{\text{TIMEpost-ibutilide: } x=0 \text{ hr} : x=1 \text{ hr}} | \text{subject, dose} = \text{maximum}(\text{QTc}_{\text{PLACEBO}}^{\text{TIMEpost-ibutilide}=xi} | \text{subject, dose}) - \text{mean}(\text{QTc}_{\text{PLACEBO}}^{\text{TIMEpost-ibutilide: } x=-0.5 \text{ hr} : x=0 \text{ hr}} | \text{subject, dose})$$

- Mean maximum change in QTc interval over the 1-hour period following the end of ibutilide infusion for each ibutilide dose

$$\text{mean}(\max_{\text{IBUTILIDE}} \Delta \text{QTc}^{\text{1hr post infusion: } x=0 \text{ hr} : x=1 \text{ hr}} | \text{dose})$$

- Mean maximum change in QTc interval over the 1-hour period following the end of ibutilide infusion for placebo

$$\text{mean}(\max_{\text{PLACEBO}} \Delta \text{QTc}^{\text{1hr post infusion: } x=0 \text{ hr} : x=1 \text{ hr}} | \text{dose})$$

- Mean change in QTc over 1-hour period following end of infusion

$$\text{mean} \Delta \text{QTc}_{\text{IBUT}}^{\text{TIMEpost-ibutilide: } x=0 \text{ hr} : x=1 \text{ hr}} | \text{subject, dose} = \text{QTc}_{\text{IBUT}}^{\text{TIMEpost-ibutilide} = xi} | \text{subject, dose} - \text{mean}(\text{predose QTc}_{\text{IBUT}} | \text{subject, dose})$$

- Data for all subjects at each dose level included in max and mean QTc calculations, regardless of whether they received a full 10-minute ibutilide infusion

### Results

- Subjects whose doses were decreased:

Center	Subject	Dose change
--------	---------	-------------

1	7,8	0.0025 mg/kg → 0.002 mg/kg
2	1,2,3	0.001 mg/kg → 0.0009 mg/kg (but later ↑ to .0015)
2	6	0.0025 mg/kg → 0.001 mg/kg
2	9	0.002 mg/kg → 0.0015 mg/kg
3	1	0.001 mg/kg → 0.0009 mg/kg (but later ↑ to .0015)
3	2	0.001 mg/kg → 0.0009 mg/kg

- Subjects who received the same dose of ibutilide twice:

Center	Subject	Dose
2	4,5	0.0025 mg/kg

- 17 of the 37 infusions in this study were terminated early
- 14 of the 17 infusion terminations were due to 2 consecutive reads of QTc > 12 msec
- There was 1 instance of 2 consecutive QTc > 12 msec for placebo

	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 <sup>a</sup>	17.5 <sup>b</sup>	-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}

<sup>a</sup> Mean change from placebo mean

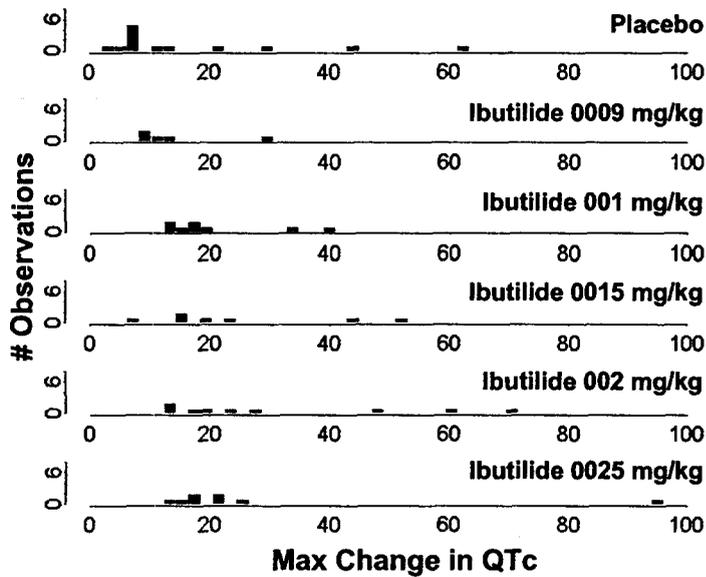
<sup>b</sup> Absolute value

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

<b>Drug / Dose</b>	<b>Range (msec)</b>
Placebo	4,62 (58 msec)
Ibutilide 0.009 mg/kg	9,29 (20 msec)
Ibutilide 0.001 mg/kg	13,40 (27 msec)
Ibutilide 0.015 mg/kg	7,52 (45 msec)
Ibutilide 0.002 mg/kg	13,70 (57 msec)
Ibutilide 0.0025 mg/kg	14,95 (81 msec)

### Range of values of maximum increase in QTc interval

- Range of maximum increase in QTc interval varied widely for each dose level. For the dose used in the LVFB trial (0.002 mg/kg), it ranged from 13-70 msec (a 57 msec difference). This is similar to the range observed for placebo (4-62 msec; a 58 msec difference).



- Variability in max change in QTc increases with increasing ibutilide dose
- The mean and median maximum increase in QTc interval differ considerably for placebo and the two highest doses of ibutilide tested.

	Placebo	Ibutilide Dose (mg/kg)				
		0.0009	0.001	0.0015	0.002	0.0025
<b>Mean</b>	17.8	14.4	21.4	25.1	32.6	28.5
<b>Median</b>	8	11	18	19	24	19.5
	(N=13)	(N=5)	(N=8)	(N=7)	(N=9)	(N=8)

- Subject 7 (Center 2) received placebo twice and had relatively high values of QTc interval increase (44 and 29 msec). Both of these measurements of QTc from subject 7 contributed to the calculation of mean maximum change in QTc. There was only one value of QTc interval increase measured in a subject in the placebo group that exceeded the measurements in subject 7. If Subject 7's placebo data are used only once, the mean value is either 16.8 or 15.6 msec, while the median value remains 8msec. A 1 or 2 second decrease in mean placebo value would correspond with a 1 or 2 second increase in change in QTc compared to placebo for each of the ibutilide doses administered.
- The mean change in QTc interval following ibutilide infusion is shown in the following table:

	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.

- When compared to mean of entire placebo data (N=13), mean prolongation of QTc interval was similar for 0.002 mg/kg and 0.0025 mg/kg tadalafil (8.6 and 9.0 msec, respectively).

#### Relevant Pharmacokinetic Information

- Maximum effect of ibutilide on QT interval usually seen immediately after the end of infusion
- No known active metabolites of ibutilide that could produce a delayed response
- Performed a literature search for the known information on ibutilide dose-response. Particularly interested in low-dose ibutilide.

The following databases were searched for Ibutilide dose and QT prolongation

PubMed (1966- )  
 Embase (1974- )  
 Derwent Drug Files (1964- )  
 Pharm-line (1978- )  
 BIOSIS (1969- )  
 IPA (International Pharmaceutical Abstracts; 1970- )  
 SciSearch (Science Citation Index; 1974- )  
 Pascal (1973- )

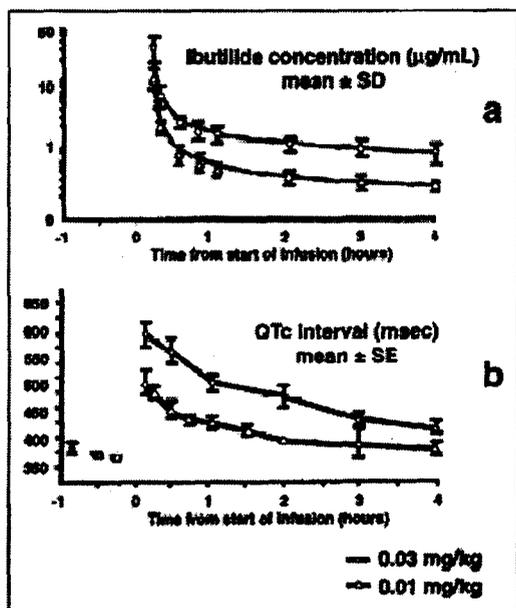
The results were as follows:

PubMed and Embase                      22 records  
 Biosis, IPA, SciSearch, and Pascal   17 records  
 Derwent Drug Files and Pharm-line   22 records

Looked over output. Limited info out there. Have info on doses that are larger, longer infusions, infusions+loading, or for outcomes other than QT/QTc. Most relevant study—JAMA study below—did not report mean change in msec. Reported mean change in AUC. Contacted author to learn more.

1. Naccarelli GV, Lee KS, Gibson JK, VanderLugt J. Electrophysiology and pharmacology of ibutilide. *Am J Cardiol* 1996; 78(8A):12-16.

“Infusion of ibutilide in humans results in a QT interval prolongation that is directly correlated with ibutilide plasma concentration (Figure 5b). The maximum QT interval prolongation is a function of both dose and rate of infusion, with the highest doses and fastest input rates causing the most QT prolongation. The QT interval peaks at the end of the infusion and rapidly returns to baseline by 2–6 hours.”



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FIGURE 5. Ibutilide: clinical pharmacologic characteristics in healthy volunteers. a: Ibutilide concentration versus infusion time. b: QT<sub>c</sub> interval versus infusion time.

2. Rodriguez I, Kilborn MJ, Liu XK, Pezzullo JC, Woosley RL. Drug-induced QT prolongation in women during the menstrual cycle. *JAMA* 2001; 285(10):1322-1326.

A volunteer sample of 58 healthy adults (38 men and 20 women) aged 21 to 40 years. INTERVENTION: A low dose of ibutilide (0.003 mg/kg), infused intravenously for 10 minutes. Subjects were monitored for 120 minutes. Women received the intervention on 3 separate occasions to correspond with menstrual cycle phases, which were verified by using hormonal assays. MAIN OUTCOME MEASURE: QT interval, recorded from electrocardiogram at timed intervals during and after ibutilide infusion and standardized for variations in heart rate (QT<sub>c</sub>).

RESULTS: Maximum (mean [SD]) millisecond increase in QT<sub>c</sub> after ibutilide infusion was greater for women during menses (63 [13]) and the ovulatory phase (59 [17]) compared with women during the luteal phase (53 [14]) and compared with men (46 [16]; P = .002 vs menses and P = .007 vs ovulation).

Measured QT intervals were corrected for heart rate using the formulae of Bazett<sup>12</sup> (QT<sub>c</sub> = QT/RR<sup>1/2</sup>) and Fridericia<sup>14</sup> (QT<sub>c</sub> = QT/RR<sup>1/3</sup>).

Ibutilide infusion induced an increase in QT<sub>c</sub> in all subjects, typically peaking within 5 minutes (t = 15 minutes) of completion of the 10-minute infusion.

Report: Mean Change in QT<sub>c</sub> Interval Area Under the Curve During the First Hour After Ibutilide Infusion

3. Wood MA, Stambler BS, Ellenbogen KA, Gilligan DM, Perry KT, Wakefield LK et al. Suppression of inducible ventricular tachycardia by ibutilide in patients with coronary artery disease. *Ibutilide Investigators. Am Heart J* 1998; 135(6 Pt 1):1048-1054.

Fifty-five patients with coronary artery disease and inducible sustained monomorphic VT at baseline received either low (0.005 mg/kg + 0.001 mg/kg, load and maintenance infusion, respectively), middle (0.01 mg/kg + 0.002 mg/kg), or high dose (0.02 mg/kg + 0.004 mg/kg) infusions of ibutilide followed by repeat programmed ventricular stimulation. The mean age of the study group was  $65.5 \pm 9.5$  years...

	<b>Low</b>	<b>Middle</b>	<b>High</b>
<b>QT</b>			
Baseline	403 ± 52	384 ± 35	371 ± 31
End load	417 ± 56	428 ± 65*	442 ± 73*
End inf	416 ± 42	410 ± 44*	440 ± 44*
<b>QTc</b>			
Baseline	425 ± 26	437 ± 28	420 ± 19
End load	463 ± 32*	488 ± 57*	507 ± 43*
End inf	458 ± 49*	484 ± 54*	496 ± 64*

Values for QT and QTc are in milliseconds for the three dosing groups at end of loading and maintenance ibutilide infusions.

*End load*, End of loading infusion; *End inf*, end of maintenance infusion.

\* $p \leq 0.05$  versus baseline for patients with both baseline and postibutilide values.

**APPEARS THIS WAY  
ON ORIGINAL**

	Low	Middle	High
<b>QT</b>			
Baseline	403 ± 52	384 ± 35	371 ± 31
End load	417 ± 56	428 ± 65*	442 ± 73*
End inf	416 ± 42	410 ± 44*	440 ± 44*
<b>QTc</b>			
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Values for QT and QTc are in milliseconds for the three dosing groups at end of loading and maintenance ibutilide infusions.

*End load*, End of loading infusion; *End inf*, end of maintenance infusion.

\* $p \leq 0.05$  versus baseline for patients with both baseline and postibutilide values.

**Table III.** Ibutilide effects on QT and QTc intervals

*From:* Wood: Am Heart J, Volume 135(6 (Part 1)).June 1998.1048-1054

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

### Note

This study report was submitted with the original filing of the NDA. It was resubmitted to note clerical changes to the document. The changes had no impact on the scientific results of the study.

### Summary/Conclusions

- Tadalafil was found to non-competitively inhibit 4'-hydroxy S-mephenytoin formation, the form-selective catalytic activity for CYP2C19, yielding an apparent  $K_i$  value of  $72.7 \pm 8.4 \mu\text{M}$ .
- In clinical studies, once-daily administration of 20 mg tadalafil for 10 days resulted in a mean  $C_{\text{max}}$  value of  $481 \mu\text{g/L}$  ( $1.24 \mu\text{M}$ ) with the highest individual plasma concentration reaching  $785 \mu\text{g/L}$  ( $2.02 \mu\text{M}$ ) (Study LVDK).
- The projected in vivo inhibition of CYP2C19 mediated metabolism, assuming a concentration of  $2.02 \mu\text{M}$  tadalafil at the active site of the enzyme, was 3%.
- These data predict that tadalafil would not cause clinically significant inhibition of the metabolic clearance of drugs metabolized by CYP2C19 under the conditions described.

### Background

CYP2C19 is a polymorphically expressed enzyme which confers a poor metabolizer phenotype in 2% to 5% of Caucasians and 13% to 23% of Asians.

### Purpose

Investigate the ability of tadalafil to inhibit the metabolism of the marker catalytic activity for cytochrome P450 (CYP) 2C19.

### Design

- Microsomes prepared from 4 human liver samples
- Following 30-minute incubations at approximately 37C, incubated samples of S-mephenytoin and microsomes, with or without the addition of tadalafil as inhibitor, were analyzed for the formation of 4'-hydroxy S-mephenytoin by HPLC. From this initial rate data, an apparent  $K_i$  value was generated.
- Incubation mixtures of 200  $\mu$ L contained human liver microsomes (0.1 mg protein) in 100 mM sodium phosphate buffer (pH 7.4), 1 mM NADPH, and S-mephenytoin (5.0, 10, 25, 50, or 100  $\mu$ M) in the absence or presence of 35, 50, 65, or 80  $\mu$ M tadalafil as inhibitor. Formation of 4'-hydroxy S-mephenytoin under these conditions was linear with respect to time.

### Planned Analyses

- The apparent kinetic parameters of  $K_m$ ,  $V_{max}$ , and  $K_i$  and the standard error of the estimated parameters were determined by nonlinear regression analysis using WinNonlin Professional, Version 3.1 (Pharsight Corporation, Mountain View, California). The untransformed inhibition data were fitted using conventional relationships for inhibition.
- Choice of the type of inhibition was determined by a number of criteria which included: visual inspection of the double reciprocal plots of the data; the random distribution of residuals; size of the sum of squares of the residuals; the standard error of the parameter estimate; and how well the  $K_m$  and  $V_{max}$  estimates with inhibitor agreed with those estimated in the absence of inhibitor.
- The predicted in vivo inhibition by tadalafil of the catalytic activities of the examined cytochromes P450 was calculated as follows:

$$\text{non-competitive inhibition: \% inhibition} = \frac{[I] * 100}{[I] + K_i}$$

- The  $K_i$  term entered into this formula was that generated in this study, and the  $[I]$  term was the highest individual plasma concentration of tadalafil following once-daily administration of 20 mg tadalafil for 10 days: 785  $\mu$ g/L (2.02  $\mu$ M) (LVDK).

### Results

- The formation of 4'-hydroxy S-mephenytoin by the human microsomal mixture in the inhibition study with tadalafil followed simple Michaelis-Menten kinetics, yielding an apparent  $K_m$  value of  $22.1 \pm 2.0$   $\mu$ M and  $V_{max}$  of  $24.1 \pm 1.5$  pmol/minute/mg protein. The best fit model describing the inhibition of the formation of 1'-hydroxy midazolam by tadalafil was found to be non-competitive, yielding an apparent  $K_i$  value of  $72.7 \pm 8.4$   $\mu$ M.
- S-mephenytoin concentrations were 5.0, 10, 25, 50, or 100  $\mu$ M. At each substrate concentration, vehicle or one of four concentrations of inhibitor was included. The concentrations of tadalafil used for the inhibition of 4'-hydroxy S-mephenytoin formation were 35, 50, 65, or 80  $\mu$ M. All incubations were performed in duplicate. The apparent  $K_i$  value represents a parameter estimate  $\pm$  the standard error of the parameter estimate.

**OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
REVIEW**

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NDA: 21-368	Submission Date(s): June 29, 2001
Brand Name	Cialis
Generic Name	Tadalafil
Reviewer	Sandip K Roy, Venkat Jarugula & He Sun
Team Leader	Ameeta Parekh
OCPB Division	DPE II
ORM division	DRUDP
Sponsor	Lilly ICOS LLC
Relevant IND(s)	IND 54,553, IND . _____
Submission Type; Code	1S
Formulation; Strength(s)	Film-coated tablet; 20 mg
Indication	Male erectile dysfunction

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## **1 Executive Summary**

Tadalafil (IC351) is a reversible inhibitor of phosphodiesterase type 5 (PDE5), the enzyme involved in specifically hydrolyzing cyclic guanosine monophosphate (cGMP). Tadalafil improves erections by enhancing the effect of nitric oxide through the inhibition of PDE5. Tadalafil has been developed as a therapy for male erectile dysfunction. Tadalafil is absorbed after oral administration with  $C_{max}$  in plasma occurring at a median  $t_{max}$  of 2 hours. At least 36% of the dose is absorbed from an oral solution. The rate and extent of absorption from the 20 mg tablet are not significantly influenced by food. As the 20 mg market image tablet used in the primary efficacy and safety trials was identical to the proposed commercial tablet, a formal bioequivalence test was not conducted. The market image 10 and 20 mg tablets used in Phase 3 trials were qualitatively identical with the drug and excipient proportional to one another.

Tadalafil is distributed into tissues, as indicated by an apparent volume of distribution of 62.6 L and 94% of the drug in plasma is bound to proteins, principally  $\alpha$  1 -acid glycoprotein and albumin. Mass balance studies suggest that tadalafil is extensively metabolized and 61% is excreted in the feces and 36% in urine. Tadalafil undergoes CYP3A4 mediated oxidation to its 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. Concentrations of methylcatechol were

of reaching the highest score for the pharmacodynamic endpoint (IIEF Q3 & Q4) is slightly higher (< 15%) at 20 mg compared to 10 mg. In study LVBF, the existence of cardiovascular conditions and weight were significant covariates. The probability of getting a score of 5 for IIEF Q4 was smaller for subjects with active cardiovascular condition at a given dose. Patients with current active cardiovascular conditions had a decrease in CL/F when compared with patients with no active cardiovascular problems (1.59 L/h vs 2.24 L/h). Creatinine clearance was a significant covariate that influenced CL/F. In study LVBG, there was a statistically significant increase in apparent volume of distribution with increasing body mass index. There was also a statistically significant increase in bioavailability with increasing Gamma-glutamyl-transferase (GGT) values and this was the only significant covariate that influenced the IIEF Q3 response scores.

Based on OCPB review and population analyses of the data submitted in support of tadalafil, it appears that the probability of reaching the highest score for the pharmacodynamic endpoint (IIEF Q3 & Q4) is slightly higher (< 15%) at 20 mg compared to 10 mg. A single 10 mg dose of tadalafil was well tolerated in healthy subjects and subjects with mild renal impairment. However, the 10 mg dose was not well tolerated in subjects with moderate renal dysfunction, prompting dose reduction to 5 mg. Due to the increased incidence of adverse events in moderately impaired subjects, no subjects with severe renal impairment received tadalafil. Thus, tadalafil dosing in patients with moderate renal impairment should be reduced by half and should be contraindicated in patients with severe renal impairment. In summary, patients with mild and moderate erectile dysfunction may benefit from availability of a lower strengths of 5 and 10 mg tadalafil and at the same time avoid risk of higher exposure in compromised renal function.

### 1.1 Recommendation

This NDA is acceptable from the OCPB perspective provided the sponsor addresses the following concerns:

- ◆ Since there is only marginal benefit (< 15%) going from 10 mg to 20 mg dose, a starting dose of 10 mg should be considered in patients with erectile dysfunction, who are otherwise healthy.
- ◆ Results of a pharmacodynamic interaction study of 10 mg tadalafil with alcohol suggested that tadalafil potentiates the hypotensive effect of alcohol. In another study conducted with 20 mg tadalafil, no clinically significant interaction was noted. However, the blood levels of alcohol were not measured in this study. Thus, we recommend an additional study of 20 mg tadalafil with 0.7 mg/kg alcohol. The sponsor should measure the blood levels of alcohol in this study.

◆

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◆ Labeling recommendations are listed as follows:

*Ketoconazole* \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

*Rifampin (and other* \_\_\_\_\_  
\_\_\_\_\_

*Antacids* \_\_\_\_\_ — Simultaneous administration  
with an antacid (magnesium hydroxide/aluminum hydroxide)  
\_\_\_\_\_

*Renal Insufficiency*— In subjects with mild (creatinine clearance 51 to 80 mL/min) or  
moderate (creatinine clearance 31 to 50 mL/min) renal impairment, \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

*Hepatic Insufficiency*—Tadalafil exposure (AUC) in subjects with mild and moderate  
hepatic impairment (Child-Pugh Class A and B) is comparable to exposure in healthy  
subjects. \_\_\_\_\_  
\_\_\_\_\_

OCPB Briefing for CIALIS was held on April 8, 10:30 AM – 11:30 AM. Following  
were the attendees:

Ashok Batra, George Benson, Mark Hirsch, Dena Hixon, Florence Houn, Venkat  
Jarugula, John Hunt, Johnny Lau, John Lazor, Larry Lesko, Peter Lee, Hank Malinowski,  
Mehul Mehta, Dornette Spell LeSane, Ameeta Parekh, Sandip Roy, Dan Shames,  
Cassandra, Michael Riel

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### 3 Summary of CPB Findings

#### *Absorption*

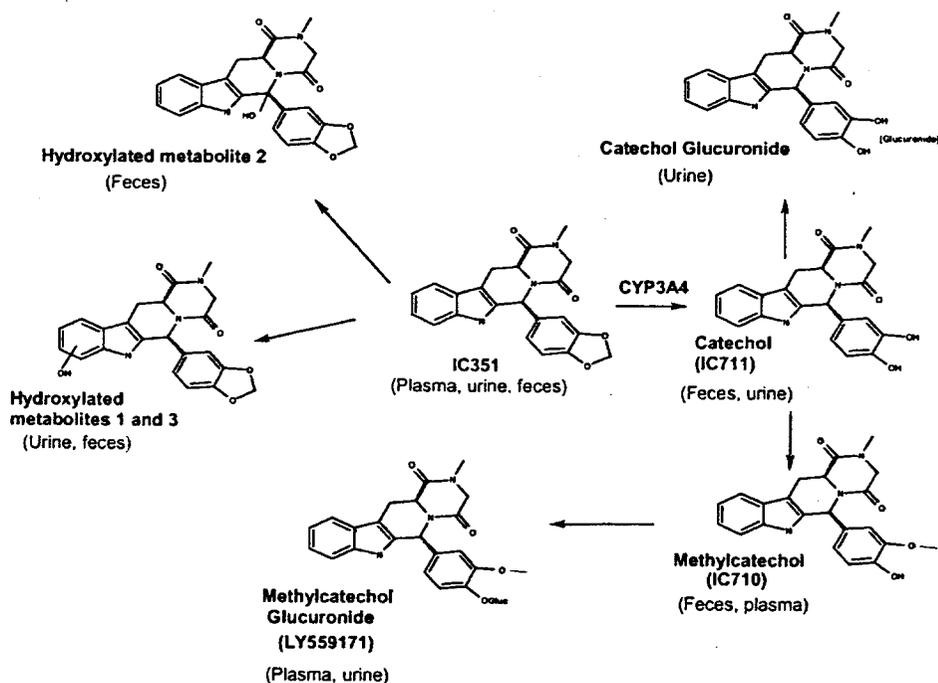
Tadalafil is absorbed after oral administration, with  $C_{max}$  in plasma occurring at a median  $t_{max}$  of 2 hours. At least 36% of the dose is absorbed from an oral solution. The rate and extent of absorption from the 20 mg tablet are not significantly influenced by food.

#### *Distribution*

Tadalafil is well distributed into tissues, as indicated by an apparent volume of distribution of  $\sim$  L and 94% of the drug in plasma is bound to proteins, principally  $\alpha$  1-acid glycoprotein and albumin.

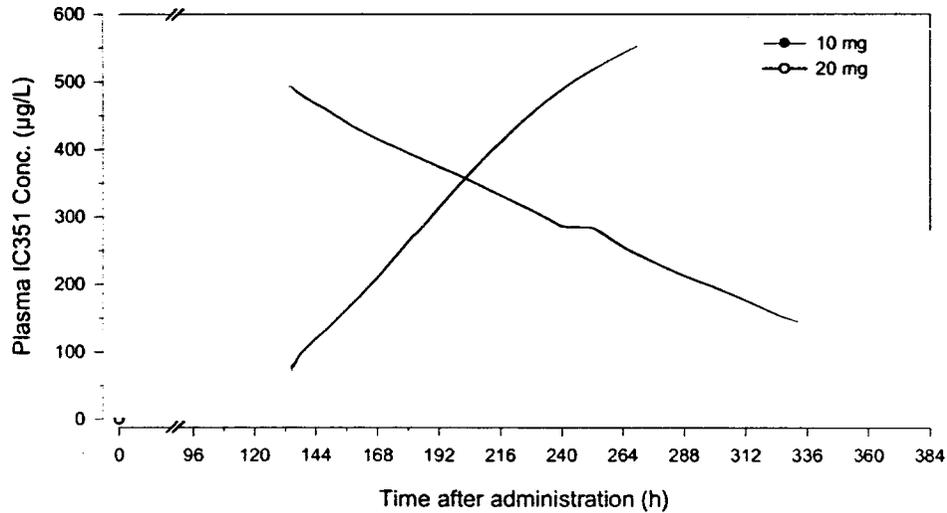
#### *Metabolism*

Mass balance studies suggest that tadalafil is extensively metabolized and 61% is excreted in the feces and 36% in urine. Tadalafil undergoes CYP3A4 mediated oxidation to its 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.



### Elimination

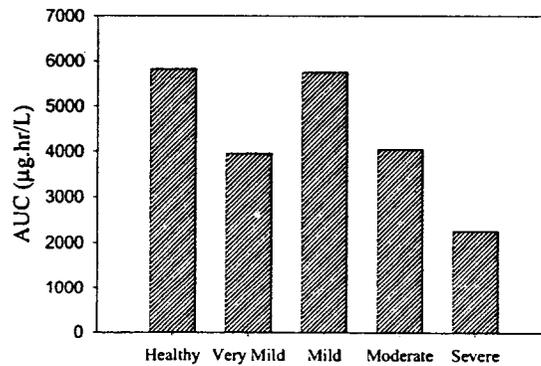
Tadalafil pharmacokinetics in patients with erectile dysfunction are essentially similar to pharmacokinetics in healthy subjects. AUC increased in a dose proportional manner across the 2.5 to 20 mg dose range, whereas increase in  $C_{max}$  was less than dose proportional at doses higher than 10 mg. Steady-state plasma concentrations are attained by Day 5 and are approximately 1.6-fold higher than the single dose values. Upon daily administration, concentrations of methylcatechol glucuronide are approximately 3-fold higher than single dose values.



### Special Population

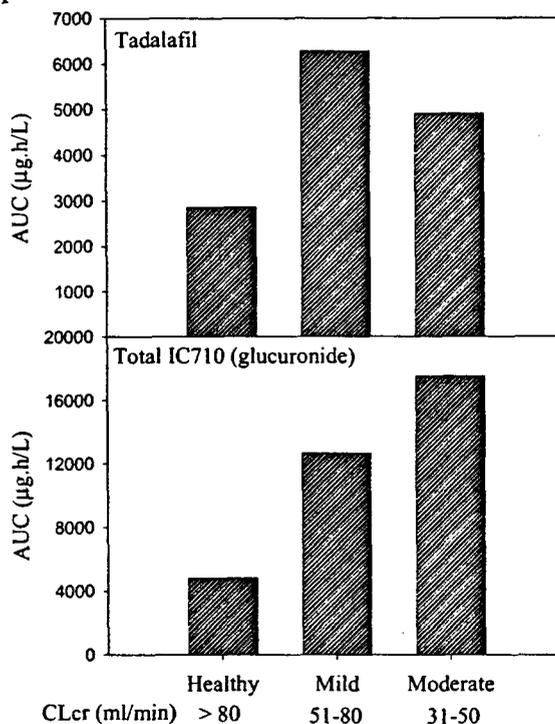
**Diabetics** – Systemic exposure, based on AUC, was reduced by approximately 19% in diabetic subjects. The decreased systemic exposure in diabetic subjects does not warrant a change in the dose for this population, because pharmacodynamic response is more or less the same in the tadalafil dose range of 10 – 20 mg.

**Hepatic impairment** – Tadalafil undergoes extensive metabolism in the liver. Thus, hepatic impairment is expected to reduce the metabolic clearance of tadalafil. However, there was no consistent trend in AUC across severity of hepatic impairment.



Mean AUC values in the patients with mild hepatic impairment were comparable to those of the healthy subjects, however, these parameters were approximately 30% lower in the very mild and moderately impaired groups. There was no consistent trend in apparent oral clearance (CL/F) across severity of hepatic impairment.

*Renal insufficiency* – Systemic exposure was ~2-fold higher in subjects with mild and moderate renal impairment following administration of 10 mg tadalafil. Renal impairment had a greater effect on the disposition of methylcatechol glucuronide than on tadalafil, as expected for a renally-cleared metabolite (see figure below). The exposure to methylcatechol glucuronide was 3.6-fold higher and was associated with higher incidence of musculoskeletal adverse events such as myalgia and back pain. The onset of these adverse events generally occurs approximately 20 hours after peak plasma concentrations of tadalafil, and when the methylcatechol glucuronide concentrations are high. Due to the increased incidence of adverse events in moderately impaired subjects, no subjects with severe renal impairment received tadalafil.



Following table summarizes treatment-emergent adverse events following administration of 10 mg tadalafil:

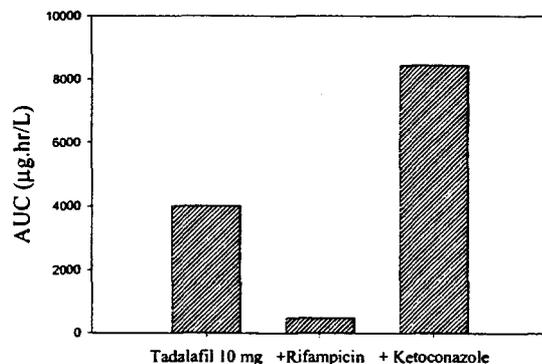
Group	Subjects with adverse events (%)
Healthy subjects	1/8 (12.5)
Mild renal impairment	1/5 (20)
Moderate renal impairment	5/6 (83.3)

The incidence of adverse events was high for patients with moderate renal impairment following administration of 10 mg tadalafil, with most of the patients reporting drug-related adverse events. Based on these results, it appears 10 and 5 mg doses may be sufficient in patients with mild and moderate erectile dysfunction, respectively. In patients with compromised renal function, a dose of 20 mg may result in even higher exposure and higher incidence of myalgia and back pain. Thus, tadalafil dosing in patients with moderate renal impairment should not exceed 5 mg and should be contraindicated in patients with severe renal impairment.

*Elderly* – In the elderly subjects (65 to 78 years), apparent clearance was reduced by approximately 20%. This was reflected in the increased exposure (approximately 25%) in the elderly subjects. Since the creatinine clearance was approximately 17% lower in the elderly subjects in this study, it appears that renal impairment can result in increased exposure of tadalafil. The increase in AUC in the elderly group was not considered to be clinically significant, therefore a change in dose is not warranted. Both young and elderly populations experienced a similar number of drug-related adverse events that were rated as moderate in severity, however two (17%) elderly subjects (but no young subjects) reported a total of three severe adverse events (one episode of pain and two episodes of myalgia) that were related to the study drug.

#### *Drug Interactions*

*In vitro* studies suggested that, tadalafil is predominantly metabolized by CYP3A4. Ketoconazole, a selective inhibitor of CYP3A4, increased tadalafil exposure by 107%. Rifampin, a CYP3A4 inducer, reduced tadalafil AUC by 88%.

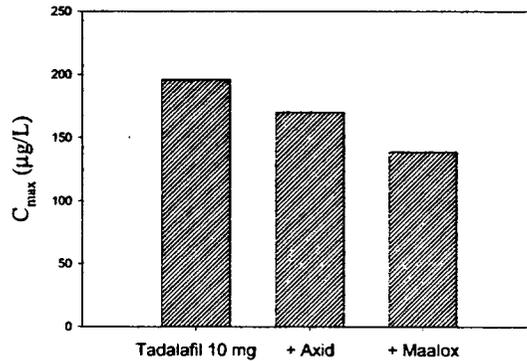


Results with cultured human hepatocytes indicated that tadalafil produces both mechanism-based inhibition of CYP3A activity and induction of CYP3A protein expression. Daily dosing of tadalafil for 14 days resulted in small reduction in AUC (13%) and increase in CL/F (14%) for midazolam. This effect may be even more pronounced with a higher dose (20 mg) tadalafil.

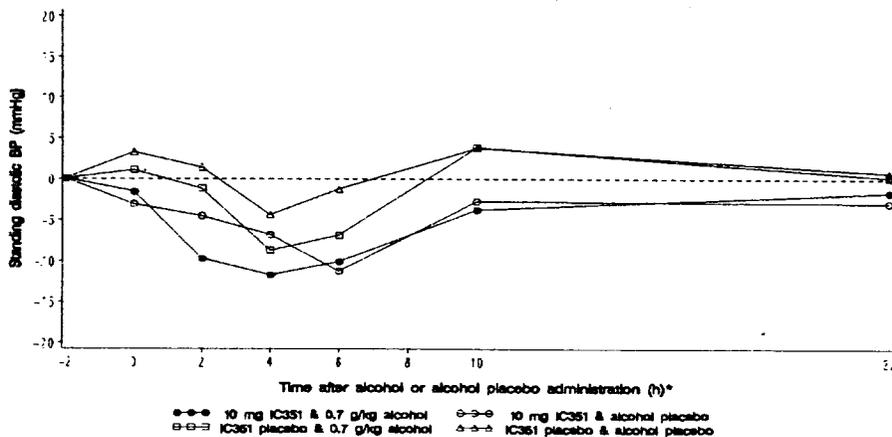
Pharmacodynamic drug-drug interaction studies were conducted with drugs that are likely to be co-administered with tadalafil. Interaction studies with nizatidine, maalox, theophylline, warfarin, metoprolol, bendrofluazide, enalapril, aspirin, isosorbide

mononitrate, and sublingual nitroglycerin used only 10 mg tadalafil. Studies with lovastatin, Angiotensin II receptor antagonists, and tamsulosin (PD) were conducted in presence of 20 mg tadalafil. Both 10 mg and 20 mg doses of tadalafil were used to investigate interaction with alcohol and the calcium channel blocker, amlodipine.

*Antacids* – When tadalafil was co-administered with Axid, mean  $C_{max}$  was reduced by 14% compared to tadalafil administered alone. Co-administration with Maalox reduced the rate of absorption of tadalafil, as indicated by a reduction in mean  $C_{max}$  (30%) and a prolongation of  $t_{max}$  (median difference 2.5 hours), compared to dosing of tadalafil alone. These results were reflected in a 14% reduction of AUC(0-24) for tadalafil administered with Maalox.



*Alcohol* – Following co-administration of 10 mg tadalafil with 0.7 mg/kg alcohol, there were trends for greater impairment of some parameters (postural stability and word recognition) compared to the administration of alcohol with tadalafil placebo. As shown in the figure below the decrease in mean standing diastolic blood pressure was larger (-12 mmHg at 4 hr) for the tadalafil and alcohol combination compared to tadalafil with alcohol placebo (-6 mmHg at 4 hr), alcohol with tadalafil placebo (-8 mmHg at 4 hr), and tadalafil placebo and alcohol placebo (-4 mmHg at 4 hr). Increases in heart rate were greatest following co-administration of tadalafil with alcohol. The overall incidence of adverse events was highest following administration of tadalafil with alcohol compared to other combinations (see individual reviews for details).



The pharmacokinetic parameters of alcohol and the corresponding dose and body weight normalized parameters for all subjects are presented in the following table:

Parameter	Treatment	
	Alcohol & 10 mg IC351 (N=16)	Alcohol & IC351 placebo (N=16)
AUC(0-3) (mg*h/mL)	160 (12.7)	158 (9.46)
AUC(0-3) <sub>norm</sub> (g*h/mL)	225 (12.3)	221 (9.73)
AUC(0-t <sub>n</sub> ) (mg*h/dL)	185 (20.2)	162 (40.6)
AUC(0-t <sub>n</sub> ) <sub>norm</sub> (g*h/dL)	261 (19.5)	227 (39.9)
C <sub>max</sub> (mg/dL)	79.3 (15.1)	76.6 (19.7)
C <sub>max, norm</sub> (g/dL)	112 (15.1)	108 (19.3)
t <sub>max</sub> (h) <sup>a</sup>	0.750	0.750
C(t <sub>n</sub> ) (mg/dL)	30.8 (16.1)	33.8 (15.2)
t <sub>n</sub> (h)	3.71 (16.2)	3.32 (26.0)

- ◆ Geometric means for AUC(0-t<sub>n</sub>), AUC(0-3) and C<sub>max</sub> for alcohol were 15%, 2% and 4% higher, respectively, following co-administration with tadalafil compared to with tadalafil placebo. All geometric mean ratios were close to one and the 90% CI for all ratios contained one, and were within 0.8 to 1.25 limits. Median t<sub>max</sub> was similar for the two treatments.
- ◆ At 3 hours post-tadalafil dose (1 hour post-alcohol or alcohol placebo dose), geometric mean plasma concentration of tadalafil following co-administration of tadalafil with alcohol was 155.2 µg/L compared to 165.3 µg/L after co-administration with alcohol placebo.

Another study was conducted in 48 male subjects to investigate the pharmacodynamic interaction between alcohol and 20 mg tadalafil. The incidence of clinically significant reductions in both supine and standing systolic and diastolic BP was similar following administration of 20 mg tadalafil or placebo with alcohol. However, the dose level of alcohol used in the present study was lower (0.6 g/kg). In the previous study, an oral dose of 0.7 g/kg resulted in blood levels (80 mg/dL) that correspond to legal intoxication as defined in the UK and in several states in the USA. The sponsor did not measure alcohol blood levels in the study conducted with 20 mg tadalafil.

*Amlodipine* – Following table shows the mean pharmacokinetic parameters of amlodipine in the presence and absence of a single dose of 10 mg tadalafil

Parameter	Amlodipine & IC351	Amlodipine & placebo
AUC(0-24) (µg*h/L)	174 (37.8)	163 (34.2)
C <sub>max</sub> (µg/L)	9.34 (36.6)	8.57 (31.3)
t <sub>max</sub> <sup>a</sup> (h)	8.00	8.00

- ◆ For AUC(0-24) and  $C_{max}$  the 90% confidence intervals of the geometric mean ratios were contained within the 0.80 to 1.25 limits.
- ◆ The plasma pharmacokinetic parameters of tadalafil are presented in the following table:

Parameter	Amlodipine & IC351
AUC(0-24) ( $\mu\text{g}\cdot\text{h}/\text{L}$ )	2761 (21.0)
$C_{max}$ ( $\mu\text{g}/\text{L}$ )	180 (21.5)
$t_{max}^a$ (h)	2.00

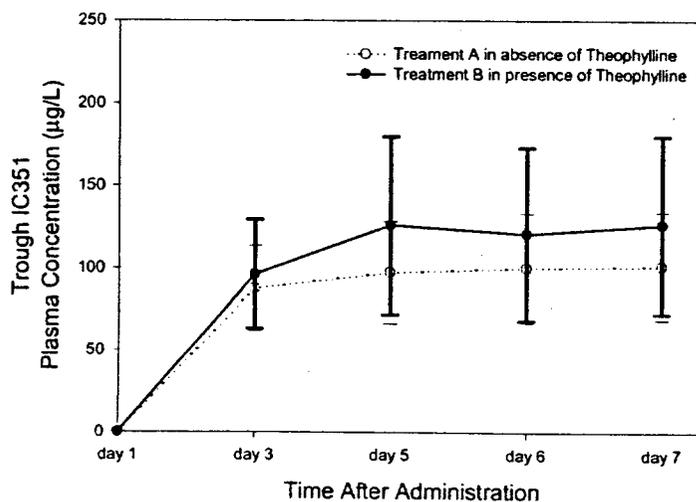
- ◆ It was concluded that co-administration of a single 10 mg dose of tadalafil had no influence on steady-state amlodipine pharmacokinetics, as AUC(0-24) and  $C_{max}$  values were equivalent. Since there was no pharmacokinetic interaction between amlodipine and 10 mg tadalafil, this was not investigated at the 20 mg dose level.

*Aspirin* – There was no evidence of potentiation of aspirin induced prolongation of bleeding time following co-administration of aspirin with placebo or tadalafil (10 mg).

*Warfarin* – AUC was reduced by 11 and 13% for (R)- and (S)-warfarin, respectively, and for both analytes  $CL/F$  and  $V_z/F$  were increased by approximately 15 and 10%, respectively, following co-administration of warfarin with steady-state tadalafil compared to placebo.  $C_{max}$  was approximately 18% lower for both (R)- and (S)-warfarin following co-administration of warfarin with steady-state tadalafil. The steady-state pharmacokinetics of tadalafil appeared not to be influenced by co-administration with a single oral dose of warfarin. There was no clinically significant difference in the pharmacodynamic effect of warfarin to increase prothrombin time following co-administration of warfarin with placebo or tadalafil.

*Theophylline* – Mean plasma concentrations were higher when tadalafil was administered with theophylline compared with theophylline placebo.

Following figure shows arithmetic mean trough (predose) plasma concentrations of tadalafil following oral daily administration of 10 mg tadalafil in the presence or absence of theophylline:



- ◆ For supine heart rate, a greater number of subjects demonstrated mean maximum values that exceeded the upper limit of the reference range following co-administration of theophylline with tadalafil (67%) compared to 57% following theophylline with tadalafil placebo and 27% following theophylline placebo with tadalafil. Following administration of theophylline placebo with tadalafil placebo only 13% demonstrated mean maximum supine heart rate values that were higher than the upper limit of the reference range.
- ◆ Increases in mean supine heart rate were larger following theophylline (6 to 7 bpm) than following tadalafil (3 to 4 bpm). When theophylline and tadalafil were given together, the increase in mean supine heart rate (8 to 12 bpm) was larger than when either treatment was given alone. This increase was generally considered additive.

*Antihypertensive agents* – At the dose of 10 mg, tadalafil potentiates the hypotensive effect of amlodipine, metoprolol, and enalapril, whereas no clinically significant pharmacodynamic interactions were noted with tamsulosin and bendrofluazide. More drug-related adverse effects were observed when each of these drugs were administered with 10 mg tadalafil than with placebo. There was clear evidence of a pharmacodynamic interaction between 20 mg tadalafil and chronically administered angiotensin AT<sub>1</sub> receptor antagonists in hypertensive subjects, based on ambulatory systolic blood pressure. More drug-related adverse effects were observed when angiotensin AT<sub>1</sub> receptor antagonists were administered with tadalafil than with placebo. No clinically significant pharmacodynamic interactions were observed, when 20 mg tadalafil was co-administered with amlodipine or tamsulosin. However, more drug-related adverse effects were observed when both these drugs were administered with tadalafil than with placebo.

*Pharmacodynamic interactions at 10 mg Tadalafil*

Interacting drug	# of Clinically significant* decreases in Blood Pressure		Subjects (%) with Drug related adverse events	
	With tadalafil	With Placebo	With Tadalafil	With Placebo
Amlodipine	16	14	27.8	5.6
Tamsulosin	Similar		5.6	0.0
Metoprolol	14	8	53.0	39.0
Bendrofluazide	Similar		38.9	22.2
Enalapril	9	6	25.0	6.3

\*include systolic and diastolic

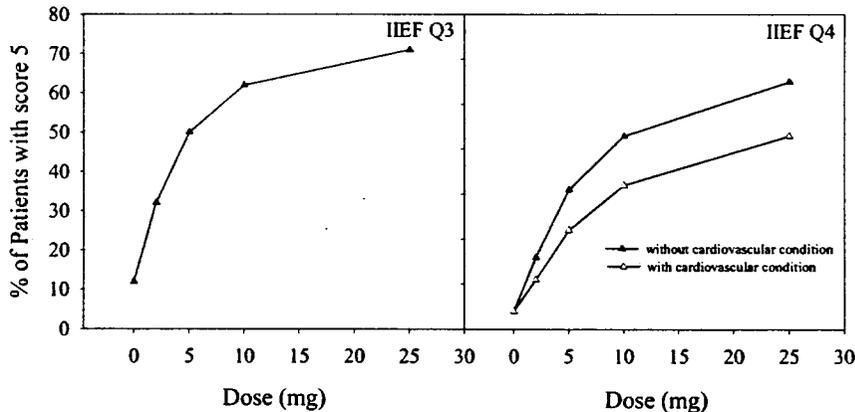
*Pharmacodynamic interactions at 20 mg Tadalafil*

Interacting drug	# of Clinically significant* decreases in Blood Pressure		Subjects (%) with Drug related adverse events	
	With tadalafil	With Placebo	With Tadalafil	With Placebo
Amlodipine	10	13	40.0	5.3
Angiotensin AT <sub>1</sub> receptor antagonist	25	14	47.1	27.8
Tamsulosin	Similar		16.7	0.0

\*include systolic and diastolic

**Population Analysis** – Population analyses were conducted in three Phase 2 studies (LVAC, LVBF and LVBG), and in one Phase 3 trial (CSR.LVCE). The objectives were to characterize the relationships between dose and efficacy and to identify patient factors and laboratory parameters accounting for patient-to-patient variability. Age, weight, creatinine clearance, liver enzyme status, cardiovascular condition, diabetes, smoking status, history of alcohol consumption were investigated as covariates. Response scores to IIEF Question 3 and Question 4 were used as endpoints in all three phase 2 studies.

- ◆ Based on the results of these studies, it appears that the probability of reaching the highest score for the pharmacodynamic endpoint (IIEF Q3 & Q4) is slightly higher (< 15%) at 20 mg compared to 10 mg.
- ◆ The general structural model was based on the pharmacologically relevant  $E_{max}$  model describing a saturable drug response with increasing dose.
- ◆ In study LVBF, the covariates that showed influence on the estimates of inter-individual variability were the existence of cardiovascular conditions and weight. As shown in the following figure, the probability of getting a score of 5 for IIEF Q4 was smaller for subjects with active cardiovascular condition at a given dose.



- ◆ In study LVBF, patients with current active cardiovascular conditions had a decrease in CL/F when compared with patients with no active cardiovascular problems (1.59 L/h vs 2.24 L/h). Covariate analyses conducted by FDA revealed creatinine clearance as a significant covariate.
- ◆ In study LVBG, there was a statistically significant increase in apparent volume of distribution with increasing body mass index. There was also a statistically significant increase in bioavailability with increasing Gamma-glutamyl-transferase (GGT) values and this was the only significant covariate that influenced the IIEF Q3 response scores.



Following are tablet ingredients as a percent of tablet weight:

Ingredient	% w/w of Core Tablet		
	5 mg Tablet	10 mg Tablet	20 mg Tablet
<b>Active Ingredient</b>			
Tadalafil	2.86%	4.00%	5.71%
<b>Other Ingredients (Granulation)</b>			
Lactose Monohydrate			
Croscarmellose Sodium			
Hydroxypropyl Cellulose			
Sodium Lauryl Sulfate			
<b>Outside Powders</b>			
Microcrystalline Cellulose			
Croscarmellose Sodium			
Magnesium Stearate			
Total (Uncoated Tablet)			
Total Weight (Uncoated Tablet)	175 mg	250 mg	350 mg

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ON ORIGINAL**

*What is the proposed mechanism of drug action and therapeutic indications?*

Tadalafil is an inhibitor of **phosphodiesterase type 5 (PDE5)**, a cGMP-specific phosphodiesterase, the major cGMP-hydrolysing enzyme in vascular smooth muscle. In the presence of activators of guanylyl cyclase, such as NO, tadalafil increases the intracellular concentration of cGMP. This leads to the relaxation of vascular and cavernosal smooth muscles that facilitates the achievement and maintenance of penile erection.

Tadalafil is being developed as a therapy for **male erectile dysfunction (MED)**, which is defined as the persistent inability to attain and/or maintain an erection adequate to permit satisfactory sexual performance

*What is the proposed dosage and route of administration?*

The proposed dosing regimen is **20 mg once daily** and intended route of administration is **oral**.

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*What efficacy and safety information (e.g., biomarkers, surrogate endpoints, and clinical endpoints) contribute to the assessment of clinical pharmacology and biopharmaceutic study data (e.g., if disparate efficacy measurements or adverse event reports can be attributed to intrinsic or extrinsic factors that alter drug exposure/response relationships in patients)?*

**Efficacy Information:**

Population pharmacokinetic/pharmacodynamic analyses were conducted on data obtained in three Phase 2 studies (LVBG, LVBF, and LVAC) and one of the primary Phase 3 efficacy studies (LVCE). Following are the pharmacodynamic endpoints used in these studies:

**International Index of Erectile Function (IIEF) questionnaire (Question 3 and Question 4):**

Response scores in these questions were used as pharmacodynamic endpoint. These questions measured the ability to penetrate and to maintain an erection during an intercourse. The scores were regarded as categorical response variables.

**Sexual Encounter Profile (SEP) diaries (Questions 2 and 3 were primary variables):**

Response scores in these questions were used only in studies LVAC & LVCE. Question 2 asked, "Were you able to insert your penis into your partner's vagina?" Question 3 asked, "Did your erection last long enough for you to have successful intercourse?" The scores were regarded as categorical response variables.

**IIEF EF Domain:**

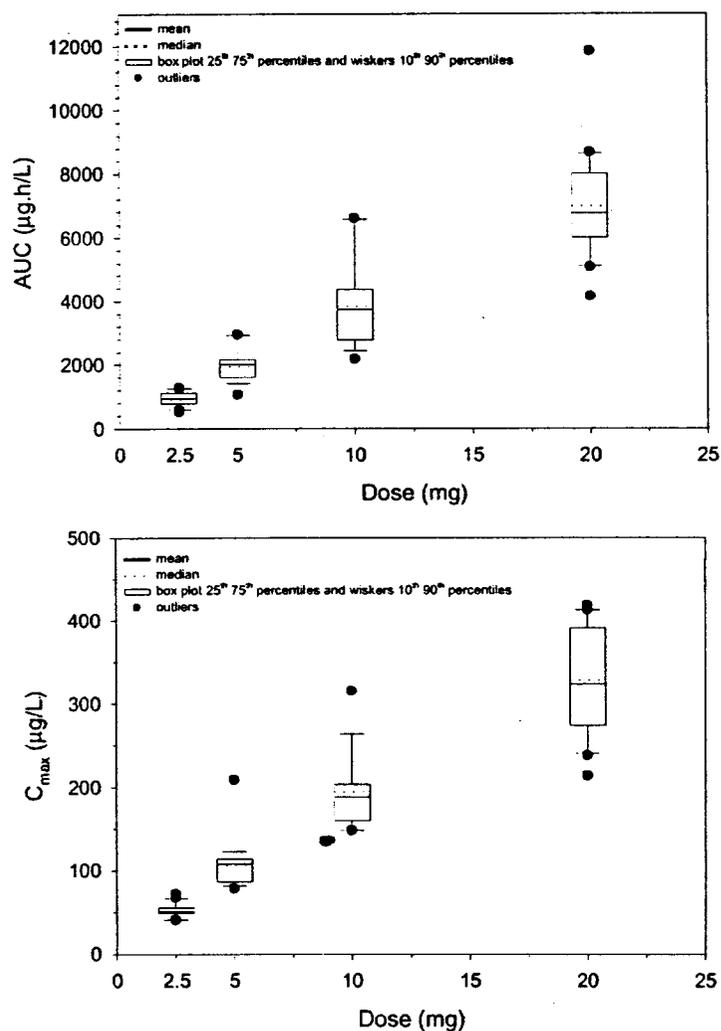
The IIEF EF Domain comprises of six questions about specific aspects of erectile function, such as whether the patient can obtain erections during sexual activity, penetrate his partner, and maintain his erections after penetrating his partner. The domain also asks the patient to assess his difficulty in achieving erections and his confidence in his ability to achieve and maintain erections. Efficacy was assessed as the change from baseline in the EF Domain score. The response scores were used only in studies LVAC & LVCE and were regarded as continuous and modeled using the traditional approach for continuous data.

## 4.2 General Clinical Pharmacology

***What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy and safety?***

*What is the degree of linearity or nonlinearity in the dose-concentration relationship?*

As shown in the figure below, the AUC increased in a dose proportional manner across the 2.5 to 20 mg dose range. On the other hand increase in  $C_{max}$  was not dose proportional across the 2.5 to 20 mg dose range.



Geometric Mean (CV%) of pharmacokinetic parameters following oral administration of a single 2.5 mg, 5 mg, 10 mg and 20 mg dose are listed in the table below:

Parameter	2.5 mg IC351 (N=16)	5 mg IC351 (N=15)	10 mg IC351 (N=15)	20 mg IC351 (N=16)
AUC ( $\mu\text{g}\cdot\text{h}/\text{L}$ )	900 (27.2)	1888 (27.5)	3647 (34.0)	6809 (24.8)
AUC(0- $t_n$ ) ( $\mu\text{g}\cdot\text{h}/\text{L}$ )	879 (27.5)	1860 (27.2)	3611 (33.3)	6762 (24.3)
AUC(0-24) ( $\mu\text{g}\cdot\text{h}/\text{L}$ )	596 (23.2)	1175 (19.4)	2265 (19.5)	4221 (16.0)
$C_{\text{max}}$ ( $\mu\text{g}/\text{L}$ )	51.6 (16.1)	103 (25.0)	190 (21.7)	322 (21.2)
$t_{\text{max}}$ (h) <sup>a</sup>	1.01	2.00	2.00	3.00
$t_{1/2}$ (h)	16.5 (30.9)	17.3 (33.5)	16.7 (34.4)	16.7 (30.2)
CL/F (L/h)	2.78 (27.2)	2.65 (27.5)	2.74 (34.0)	2.94 (24.8)
$V_z/F$ (L)	66.0 (20.3)	66.0 (26.0)	66.1 (19.2)	70.9 (17.9)

There was an increase in median  $t_{\text{max}}$  across the dose range (from 1 to 3 hours). For  $t_{1/2}$ , CL/F and  $V_z/F$ , estimates of  $\beta$  were all close to zero and the 95% confidence intervals all included zero, indicating that these parameters were independent of dose across the 2.5 to 20 mg dose range.

*How do PK parameters change with time following chronic dosing?*

Steady-state in the pharmacokinetics of tadalafil was attained by Day 5 following administration of 10 and 20 mg once daily for 10 days. Steady-state plasma tadalafil concentrations during once-daily dosing for 10 days were approximately 1.6-fold higher and concentrations of total methylcatechol in hydrolysed plasma (predominantly the methylcatechol glucuronide) were approximately 3-fold higher than single dose values. Following figure shows mean ( $\pm$ SEM) tadalafil concentrations following once-daily administration of 10 and 20 mg doses.

