The estimates of accumulation based on $AUC_\tau$ (approximately 1.6-fold for 10 and 20 mg) were comparable to the expected accumulation index of 1.63. The mean values for $t_{1/2}$, CL/F and Vz/F were consistent with single dose values and indicated an absence of auto-induction or auto-inhibition of metabolism. The steady-state PK parameters of tadalafil following once-daily administration of a 20 mg dose are presented in the table below:

| | Geometric mean (CV%) | | |
|---|---|---|---|
| **Parameter** | **Day 1 (n=15)** | **Day 5 (n=15)** | **Day 10 (n=13)** |
| $AUC_\tau$ (μg*h/L) | 4950 (23.0) | 7692 (31.1) | 7389 (38.2) |
| $C_{max}$ (μg/L) | 352 (24.5) | 514 (26.8) | 481 (31.0) |
| $t_{max}$ (h)[a] | 2.0 | 2.0 | 2.0 |
| $t_{1/2}$ (h) | - | - | 18.7 (40.4) |
| CL/F (L/h) | - | 2.6 (31.1) | 2.71 (38.2) |
| $V_z/F$ | | - | 73.1 (22.9) |
| Accumulation Ratio[b] for $AUC_\tau$ | | 1.58 | 1.55 |
| Accumulation Ratio[b] for $C_{max}$ | | 1.49 | 1.41 |

[a] Median (min-max) data.

[b] Geometric LS mean.

Another study (Study LVAU) was conducted, where 12 healthy male subjects first received a 5 mg tablet as a single dose and, after a washout period, received a 5 mg tablet once-daily for 10 days. The second group of 12 subjects received 10 mg tablets in the same manner. Steady state was not achieved in this study because mean $AUC_\tau$ was 19% higher on Day 10 than on Day 5.

*What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?*

Following table summarizes inter-subject and intra-subject variability analyzed using body mass index as a covariate:

| Parameter | Inter-subject CV% | Intra-subject CV% |
|---|---|---|
| AUC | 37.4 | 13.3 |
| $C_{max}$ | 25.1 | 15.8 |
| $t_{½}$ | 25.5 | 7.87 |
| CL/F | 37.4 | 13.3 |
| $V_z/F$ | 24.3 | 14.7 |

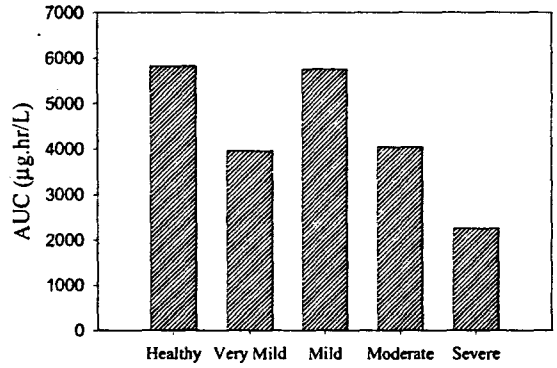
A statistically significant decrease in CL/F and an increase in Vz/F with increasing body mass index (BMI) was detected using linear mixed-effects models. Statistically significant effects of age, gender, and smoking status (104 smokers) could also be detected. However, the percentage of total inter-subject variability explained by these factors was small (<12%), suggesting that they could not account for much of the difference between individuals. Population pharmacokinetic analysis (study LVCE) identified the hepatic enzyme gamma glutamyl transferase (GGT) as a covariate having a statistically significant influence on CL/F.

4.3 Intrinsic Factors

## *What intrinsic factors influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?*

*Hepatic impairment*

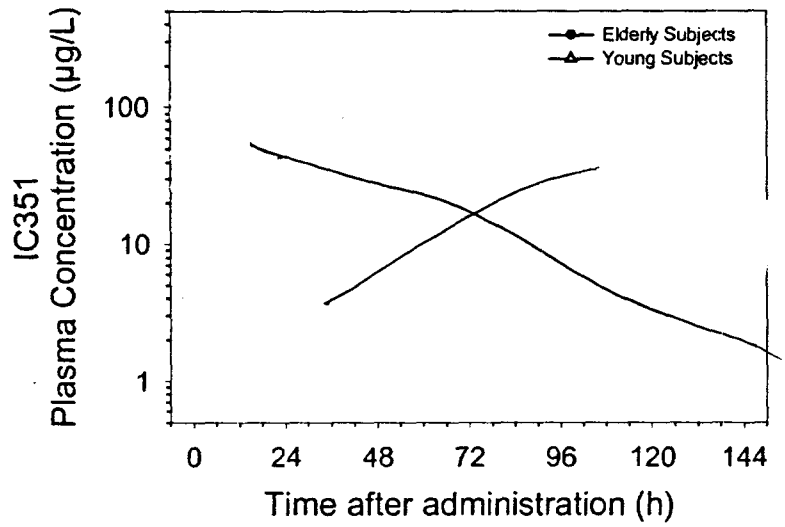
Since elimination of tadalafil is predominantly via hepatic metabolism, it is important to define the effects of hepatic impairment on the pharmacokinetics of tadalafil. Thus, an open-label, parallel group study was conducted in 8 healthy subjects and 25 patients with varying degrees of hepatic impairment (eight with very mild, mild and moderate impairment, one with severe impairment). The study compared the pharmacokinetics of tadalafil in these populations, following a single oral 10 mg dose.




- 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. The AUC value for the single patient with severe hepatic impairment was comparable to the lowest individual values for the other groups.
- There was no consistent trend in apparent oral clearance (CL/F) across severity of hepatic impairment.
- The apparent volume of distribution (Vz /F) appeared to increase with increasing severity of impairment. An approximately 2-fold increase in Vz /F compared to the geometric mean value for healthy subjects was found for the moderately impaired group.
- Terminal half-life values tended to be prolonged and more variable across individuals with hepatic impairment.

*Age:*

An open-label, parallel group study was conducted in 12 elderly and 12 young male subjects in order to study the effect of age on the pharmacokinetics of tadalafil following a single 10 mg oral dose, and to further assess the safety and tolerability of tadalafil. Following figure shows plasma concentration-time profiles following a 10 mg single oral dose to 12 elderly subjects or 12 young subjects.

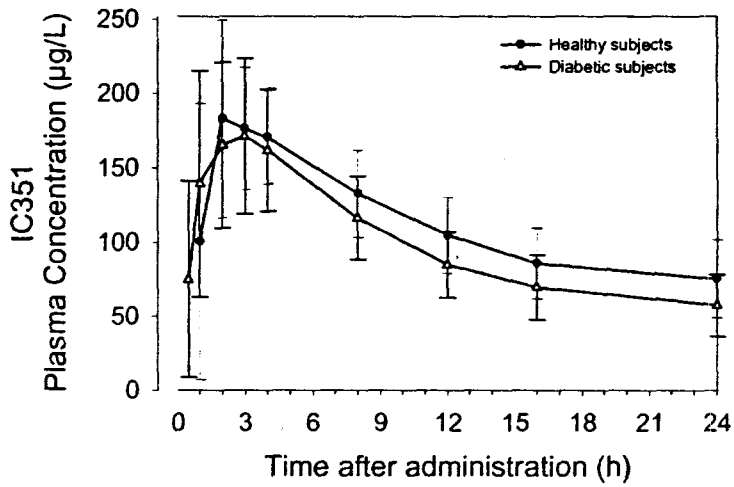



- Apparent clearance was reduced by approximately 20% in the elderly subjects. This was reflected in the increased exposure (approximately 25%) in the elderly subjects. Since the creatinine clearance was approximately 17% lower in the elderly subjects in this study, it appears that renal impairment can result in increased exposure of tadalafil.
- As $C_{max}$, $t_{max}$ and AUC(0-24) were slightly higher in elderly group compared to the younger subjects, this suggests that the rate and extent of drug absorption within this period were not much different between the two groups.
- The major difference in the concentration-time profiles was in terms of the terminal elimination half-life, the mean half-life in the elderly group was approximately 5 hours longer than that of the young group.
- Both 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.
- The increase in AUC in the elderly group was not considered to be clinically significant, therefore a change in dose is not warranted. However, this study was conducted at 10 mg dose, therefore the proposed dose of 20 mg may not be appropriate for elderly.

*Diabetes*

An open-label, parallel group study was conducted in 12 diabetic and 12 healthy subjects to compare the pharmacokinetics of tadalafil in these populations, following a single oral 10 mg dose (Study LVAS).

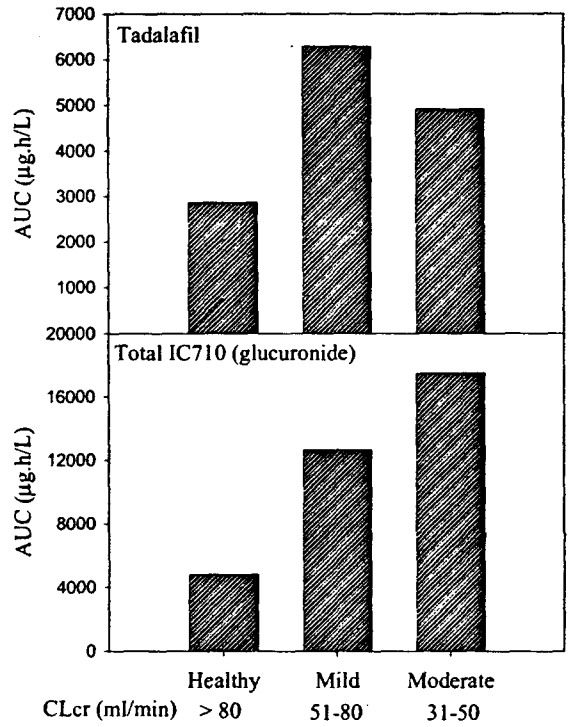
Arithmetic mean (±SD) plasma concentration-time profiles (linear scale) of tadalafil after oral administration of a single 10 mg dose in diabetic subjects (n=12) and healthy subjects (n=12) are presented in the following figure:




- Mean values for AUC was approximately 19% lower when tadalafil was administered to diabetic subjects.
- Mean CL/F was approximately 23% higher in diabetic subjects, reflecting the reduced systemic exposure (AUC) in this group.
- The mean terminal half-life was approximately 3 hours shorter in diabetic subjects compared to healthy subjects.
- Dose adjustment is not necessary in diabetic subjects.

*Renal Impairment*

- Mean tadalafil AUC increased by approximately 2- fold and $C_{max}$ by approximately 1.3- fold in patients with mild and moderate renal impairment compared to healthy subjects. Apparent oral clearance (CL/F) was reduced in the renally impaired subjects, which resulted in a longer apparent $t_{1/2}$.
- Mean exposure (AUC) for total IC710 (methylcatechol glucuronide) appeared to increase in relation to renal impairment, with the more pronounced effect being in patients with moderate renal impairment. The parameter AUC was approximately 3.6- fold and 2.6- fold higher in moderate and mild renally impaired subjects. The parameter $C_{max}$ also increased with the degree of renal impairment, being approximately 1.6- and 1.3- fold higher for patients with moderate and mild renal impairment, respectively.




Geometric mean (CV%) pharmacokinetic parameters of tadalafil after oral administration of a single 10 mg dose in healthy subjects and patients with renal impairment are shown in the following table:

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

Following table summarizes geometric mean (CV%) pharmacokinetic parameters of total IC710 (methylcatechol glucuronide) after oral administration of a single 10 mg dose in healthy subjects and patients with renal impairment:

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

- AUC range for tadalafil was larger at creatinine clearances of less than approximately 70 mL/min. For total IC710, a nonlinear association between individual dose normalized AUC values and creatinine clearance was apparent, with AUC increasing as creatinine clearance decreased.
- The 10 mg dose of tadalafil was reasonably well tolerated in healthy subjects and subjects with mild renal impairment. In subjects with moderate renal impairment, however, there was an increased frequency of pain and myalgia. The 5 mg dose was well tolerated in all groups. 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:

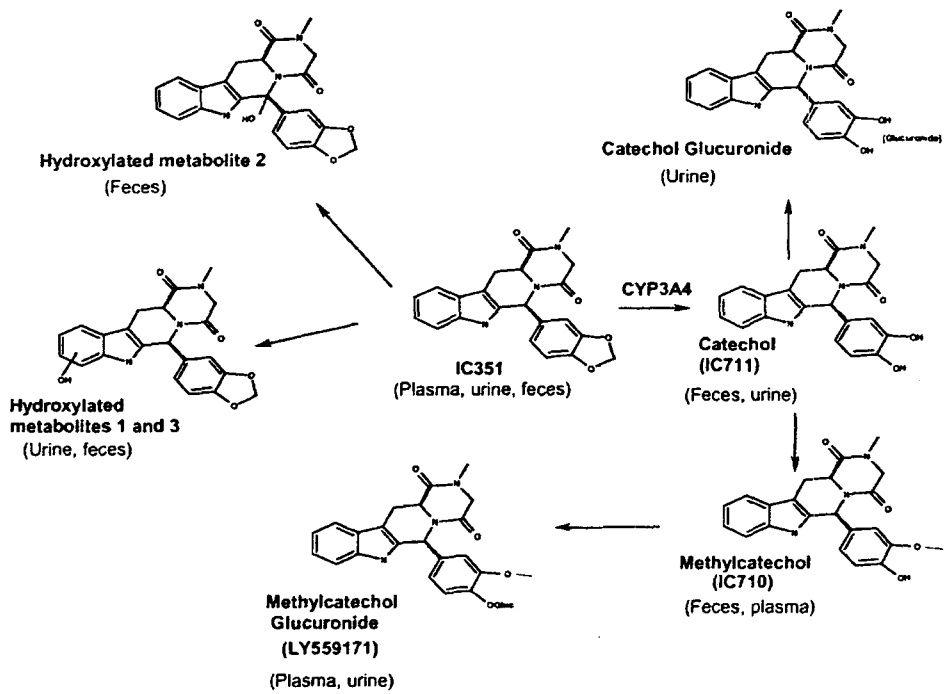
| Group | Subjects with adverse events (%) |
|---|---|
| Healthy subjects | 1/8 (12.5) |
| Mild renal impairment | 1/5 (20) |
| Moderate renal impairment | 5/6 (83.3) |

The incidence of drug-related 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.

*Do mass balance studies suggest that renal or hepatic elimination is significant? If so, how does the exposure and/or exposure-response change with renal or hepatic function?*

The disposition and biotransformation of tadalafil was examined in a study (LVAA) in which a single dose containing approximately 100 μCi of [$^{14}$C]-tadalafil (approximately 100 mg) was administered to 6 healthy male subjects as a solution in PEG 400. Samples of urine, feces, expired air, semen, and blood were collected. The mean total recovery of the radiolabel was approximately 97% within 312 hours of dosing, with the majority of radioactivity (92%) being recovered within 144 hours. Approximately 61% of the total radioactive dose was recovered in feces, whilst approximately 36% was excreted in urine. urinary recovery of unchanged tadalafil was less than 0.3% of the dose.

Following figure shows the proposed biotransformation pathways of tadalafil in healthy humans subjects:




It appears tadalafil undergoes extensive metabolism in the liver. Thus, hepatic impairment is expected to reduce the metabolic clearance of tadalafil. However, mild and moderate hepatic impairment did not compromise metabolic clearance of tadalafil and systemic exposure (AUC) to tadalafil was similar across subject groups. On the other hand, systemic exposure was ~2-fold higher in subjects with mild and moderate renal impairment. Renal impairment had a greater effect on the disposition of methylcatechol glucuronide than on tadalafil, as expected for a renally-cleared metabolite. Mean AUC of total IC710 (methylcatechol glucuronide) was approximately 3.6- fold and 2.2- fold higher in moderate and mild renally impaired subjects, respectively.

4.4 Extrinsic Factors

## *What extrinsic factors influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?*

*Is there an in vitro basis to suspect in vivo drug-drug interactions?*

The potential of tadalafil to inhibit cytochrome P450-mediated metabolism was evaluated *in vitro*. A study was conducted with human liver microsomes to evaluate the potential for tadalafil to demonstrate mechanism-based inhibition. These data indicated that tadalafil inhibits human CYP3A activity in a time- and concentration-dependent manner, suggesting mechanism-based inhibition. The maximum inhibition was 76% following a 60 minute pre-incubation of human liver microsomes with 25 μM (9700 μg/L) tadalafil and NADPH. Tadalafil inhibited CYP1A2, CYP2C9, and CYP3A, with apparent $K_i$ values of [redacted] respectively. Once-daily administration of 20 mg tadalafil for 10 days resulted in a mean $C_{max}$ value of 481 μg/L (1.24 μM); the highest individual plasma concentration was 785 μg/L (2.02 μM). With tadalafil concentration of 2.02 μM at the active site of the enzymes, the projected *in vivo* inhibition of metabolism mediated by CYP3A4, CYP2C9, and CYP1A2 was 4.7%, 3.0%, and 12.8%, respectively. The $I/K_i$ ratio for CYP3A4 was 0.05, which indicated that the likelihood of an interaction is remote. Results with cultured human hepatocytes indicated that tadalafil produces both mechanism-based inhibition of CYP3A activity and induction of CYP3A protein expression.

*Is the drug a substrate of CYP enzymes?*

The role of various cytochrome P450 enzymes in the biotransformation of tadalafil to the catechol metabolite was extensively studied *in vitro*. The overall results clearly demonstrate that CYP3A4 is the predominant enzyme involved in forming this metabolite. However, additional isoforms were found to be capable of forming this metabolite, albeit at significantly reduced capacity compared to CYP3A4. Using individual recombinant cytochrome P450 enzymes in incubations with tadalafil, it was demonstrated that CYP3A4 formed the catechol metabolite at rates 13-fold, 14-fold, 25-fold, and 25-fold greater than CYP2C9, CYP2C8, CYP2C19, and CYP2D6, respectively.

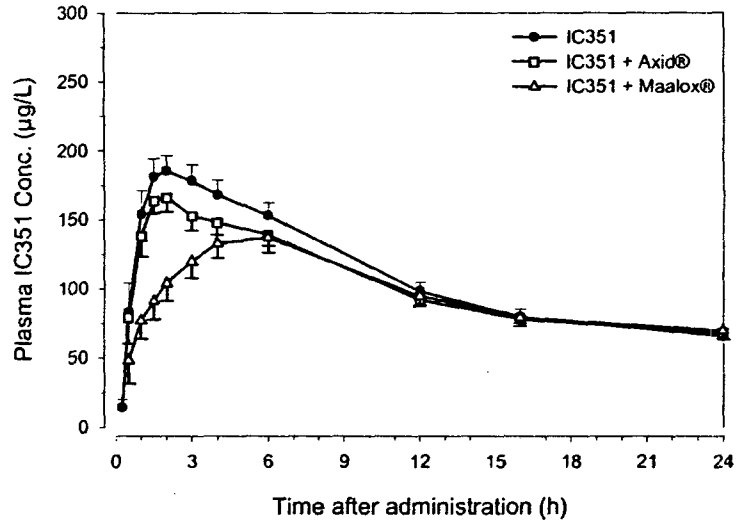
*Is the drug an inhibitor and/or an inducer of CYP enzymes?*

Results with cultured human hepatocytes indicated that tadalafil produces both mechanism-based inhibition of CYP3A activity and induction of CYP3A protein expression. An open-label study was conducted in twelve healthy male subjects to determine the effects of single and multiple oral doses of 10 mg tadalafil on the pharmacokinetics of oral midazolam (Study LVAF). The small reduction in AUC and increase in CL/F for midazolam together with the lower plasma concentrations for tadalafil indicate that tadalafil may be a mild inducer of CYP3A4. This effect may be even more pronounced with a higher dose (20 mg) tadalafil.

*What other co-medications are likely to be administered to the target patient population?*

**$H_2$ Antagonists and Antacids**

- When 10 mg tadalafil co-administered with 300 mg Axid, mean $C_{max}$ was reduced by 14% compared to tadalafil administered alone. The lower 90% CI for the ratio fell just outside the lower limit of 0.80, which may suggest an interaction between tadalafil and Axid.
- There was no evidence of an effect on AUC following co-administration of tadalafil with Axid, as the geometric LS means were similar and the 90% CI for the ratio fell within the 0.8 to 1.25 limits.
- There was evidence that co-administration with 20 ml Maalox reduced the rate of absorption of 10 mg 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.
- The 90% CI of geometric mean ratio for $C_{max}$ was outside the 0.80 to 1.25 limits. Median t max occurred approximately 2.5 hours later following dosing of tadalafil with Maalox, compared to tadalafil alone, and the 90% CI for the median difference excluded zero. However, the 90% CI for the geometric mean AUC ratios were within the 0.80 to 1.25 limits.




- Administration of Maalox had no apparent effect on gastric pH but significantly reduced the rate of absorption tadalafil. Conversely, co-administration with Axid markedly increased gastric pH but had little effect on the pharmacokinetics of tadalafil. These results imply that a non-pH-related phenomenon was the cause of the reduced absorption of tadalafil following co-administration with Maalox.

**Aspirin**

This was an Investigator and subject-blind, randomized, parallel group study (LVBV) to investigate the safety, tolerability and effect on bleeding time of the oral tadalafil. It was intended that 28 subjects were to receive a once-daily oral dose of 300 mg aspirin over 5 days with 14 subjects receiving 10 mg tadalafil and 14 receiving placebo with the final dose of aspirin on Day 5.

Mean bleeding time data are presented in the following table:

| | Day 1 | Day 5 | |
|---|---|---|---|
| Treatment | Predose (mins) | Predose (mins) | 3 h postdose (mins) |
| 300 mg aspirin and placebo | 4.45 (0.652) | 8.45 (3.10) | 9.57 (5.88) |
| 300 mg aspirin and 10 mg IC351[a] | 4.40 (1.10) | 7.52 (1.84) | 7.73 (2.16) |

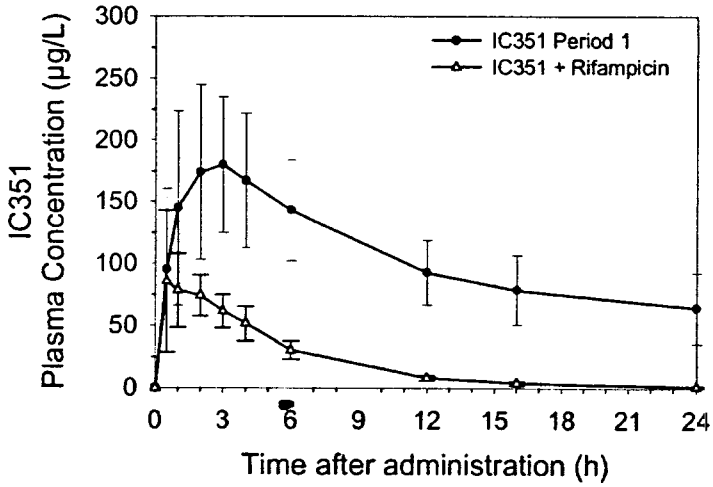
- Mean bleeding time was increased by approximately 2-fold following once-daily dosing with 300 mg aspirin for 4 consecutive days.
- There was no evidence of potentiation of aspirin induced prolongation of bleeding time following co-administration of aspirin with placebo or tadalafil (10 mg) on day 5, with the ratios of the mean bleeding times at 3 hours postdose to predose being similar and close to unity for both treatment groups.

*Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?*

**Rifampicin & Ketoconazole**

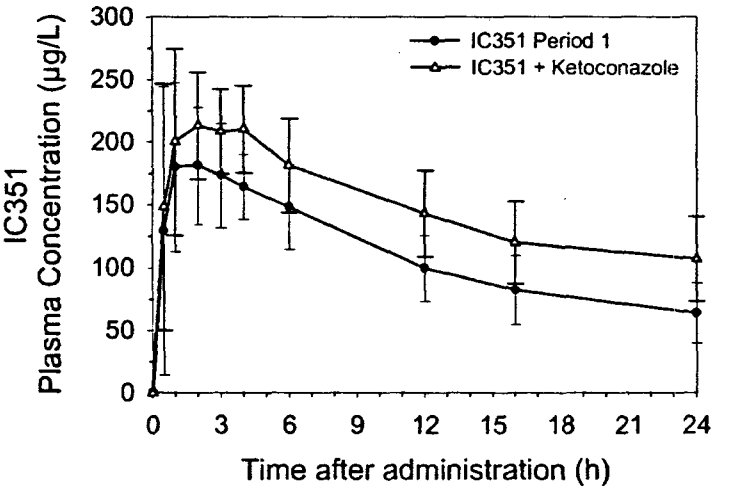
A Phase I, open-label, randomized, two period study in two distinct parts was conducted in 36 healthy male subjects to compare the pharmacokinetics of tadalafil in the presence and absence of a known CYP3A4 inducer (rifampicin) in Part A of the study, and in the presence and absence of a known CYP3A4 inhibitor (ketoconazole) in Part B. In Treatment Period 1, all subjects received a single dose of tadalafil. In Treatment Period 2 in each part of the study, 12 subjects were scheduled to receive tadalafil in combination with the interaction drug (the active group) while 6 subjects were scheduled to receive tadalafil alone (the control group). Thirty-one of the 36 subjects completed the study.

- In the presence of rifampicin, geometric mean apparent clearance (CL/F) was increased approximately 8.5-fold, which is reflected in a decrease in geometric mean half-life, 3.65 hours compared to 16.7 hours when tadalafil was administered alone.
- For AUC, AUC(0-24) and $C_{max}$, geometric means were 88, 81 and 46% lower for tadalafil co-administered with rifampicin compared to tadalafil administered alone. This reduction was clinically significant, as the 90% CI for the ratios fell outside the predefined equivalence limits of 0.7 to 1.43, which were selected for their clinical relevance.
- Median $t_{max}$ for co-administration with rifampicin occurred significantly earlier (1.25 hours) than when tadalafil was administered alone.




- Decrease in exposure to tadalafil when co-administered with rifampin however did not result in decrease in number of drug-related adverse events.
- In the presence of ketoconazole, geometric mean CL/F was decreased by approximately 50%, which is reflected in an increase in geometric mean half-life, 30.4 hours compared to 15.9 hours when tadalafil was administered alone.

- For AUC, AUC(0-24) and $C_{max}$, geometric means were 107, 35 and 15% greater for tadalafil co-administered with ketoconazole compared to tadalafil administered alone.




- Headache, myalgia and back pain were the drug-related adverse events most commonly reported in this study. There was an increase in the number of these drug-related adverse events when tadalafil was administered with ketoconazole (64% vs 40%).

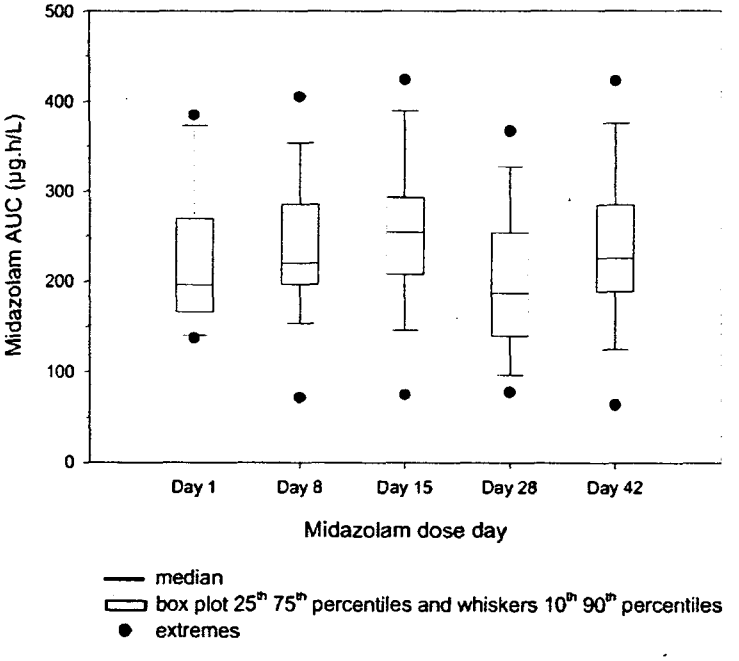
**CYP3A4 substrates**

*In vitro* data suggested that tadalafil could inactivate CYP3A4 in a time- and concentration-dependent manner. The possibility that tadalafil might be a mechanism-based inhibitor of CYP3A4 was investigated with the CYP3A4 probe substrates midazolam and lovastatin as indicated in the following sections.

*Midazolam* – Midazolam is a short acting benzodiazepine which is almost completely eliminated via CYP3A4 enzyme-mediated metabolism. It is therefore considered to be a sensitive *in vivo* probe of CYP3A4 activity. After oral administration, midazolam undergoes extensive first pass metabolism in the intestinal wall and liver and, therefore, its pharmacokinetics are markedly altered by inhibition and induction of CYP3A4. Therefore, an open-label study was conducted in twelve healthy male subjects to determine the effects of single and multiple oral doses of 10 mg tadalafil on the pharmacokinetics of oral midazolam.

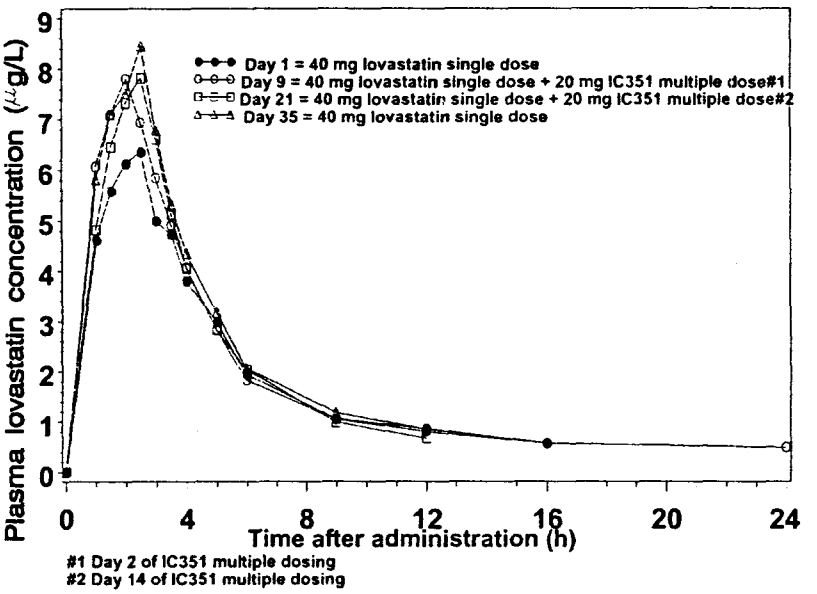
Subjects received a single oral dose of 15 mg midazolam on five occasions: administered alone on two occasions (Days 1 and 8); 3 hours after a single dose of 10 mg tadalafil (Day 15); 3 hours after the last dose of a 14 day once-daily 10 mg tadalafil multiple dosing regimen (Day 28); and 14 days after the last dose of tadalafil (Day 42).

- Daily dosing of 10 mg 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 proposed higher dose of 20 mg tadalafil.



*Lovastatin* – Lovastatin, a CYP3A4 substrate, is an inactive lactone which is readily hydrolyzed in the liver to the active β-hydroxyl form. It undergoes extensive first pass metabolism in the liver and less than 5% of the oral dose has been reported to reach the circulation. Pharmacokinetics of oral lovastatin (40 mg) were studied in the same subjects prior to and during 14 days of tadalafil multiple dose administration and 14 days after the final dose of tadalafil. Thus, an open-label study was conducted in healthy male and female subjects (10 females and six males) to investigate the effects of single (20 mg) and multiple oral doses (20 mg once daily) of tadalafil on the pharmacokinetics of oral lovastatin (study LVDM). Subjects received a single oral dose of 40 mg lovastatin co-administered with food on four occasions in order to maximize its absorption. Lovastatin was administered alone on Day 1 and Day 35 and was given with tadalafil on Day 9 and Day 21 (Day 2 and 14 of the tadalafil dosing regimen).

Following figure shows arithmetic mean plasma concentration versus time profiles of lovastatin in healthy subjects receiving a single 40 mg oral dose on days 1, 9, 21 and 35 (N=16).




Following table shows geometric mean (CV%) pharmacokinetic parameters of lovastatin following a single oral dose (40 mg) on days 1, 9, 21 and 35:

| Parameter | Day 1 (N=16) | Day 9 (N=16) | Day 21 (N=16) | Day 35 (N=16) |
|---|---|---|---|---|
| AUC (µg*h/L) | 30.8 (95.5)[a] | 43.8 (66.6)[a] | 34.4 (48.3)[b] | 44.1 (64.8)[a] |
| AUC(0-$t_n$) (µg*h/L) | 31.4 (76.3) | 36.2 (52.1) | 32.5 (69.4) | 36.3 (78.5) |
| $C_{max}$ (µg/L) | 7.62 (47.1) | 8.38 (43.6) | 8.82 (49.9) | 8.93 (70.0) |
| $t_{max}$ (h)[c] | 2.50 | 1.75 | 2.00 | 2.50 |

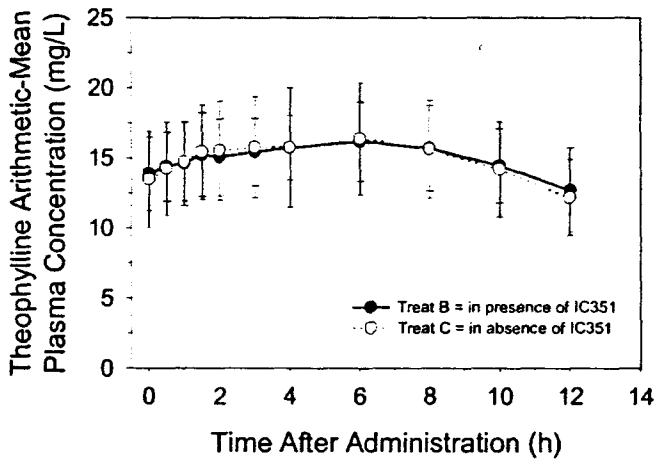
[a]N = 10
[b]N = 9

- Based on the 'no effect' boundary of 0.5 to 2.0 pre-specified by the sponsor, pharmacokinetics of the CYP3A4 probe substrate lovastatin were not altered when co-administered with tadalafil for 14 days.

**CYP1A2 Substrate**

*Theophylline* – A Phase I, subject and Investigator blind, placebo-controlled, randomized, four period crossover study (Study LVAP) was conducted in a total of 17 healthy young male subjects in order to examine the effect of tadalafil on the pharmacodynamics and pharmacokinetics of theophylline, and to further assess the safety and tolerability of tadalafil. The primary pharmacodynamic endpoint of this study was to define the putative potentiating effect of tadalafil on the heart rate response to theophylline.

Following figure shows mean plasma concentration-time profiles at steady-state (Day 7) following oral BID administration of theophylline in the presence and absence of tadalafil:

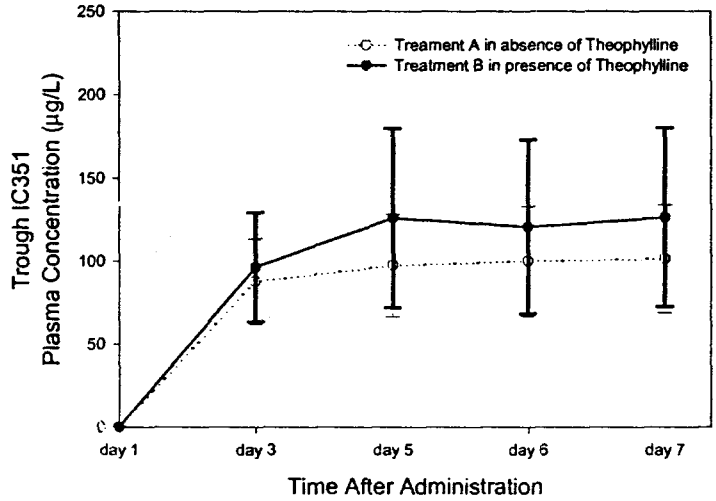



Selected pharmacokinetic parameters of theophylline are summarized in the following table:

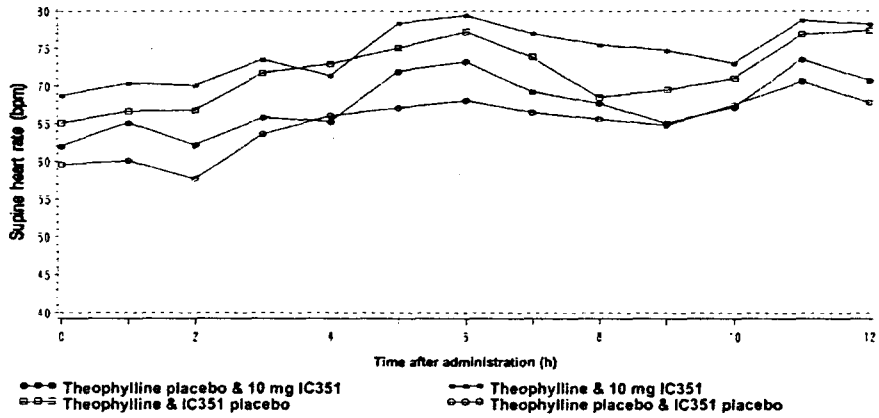
| Parameter | Treatment | |
|---|---|---|
| | Theophylline & 10 mg IC351 | Theophylline & IC351 placebo |
| $AUC_{\tau,ss}$ (mg*h/L) | 175 (13.7) | 177 (22.4) |
| $AUC_{\tau,ss,norm}$ (kg*h/L) | 25.5 (29.5) | 25.8 (36.9) |
| $C_{max,ss}$ (mg/L) | 16.6 (14.2) | 16.7 (22.8) |
| $C_{max,ss,norm}$ (kg/L) | 2.42 (28.8) | 2.43 (35.4) |
| $t_{max,ss}$ (h)[a] | 4.00 | 4.00 |
| $PTF_{ss}$ (%) | 29.2 (40.9) | 31.6 (24.6) |
| $C_{av,ss}$ (mg/L) | 14.6 (13.7) | 14.8 (22.4) |
| $C_{av,ss,norm}$ (kg/L) | 2.13 (29.5) | 2.15 (36.9) |
| $CL/F_{ss}$ (L/h) | 3.12 (26.7) | 3.09 (31.8) |
| $CL/F_{ss}$ (L/h/kg) | 0.0392 (29.5) | 0.0388 (36.9) |

Plasma concentrations of tadalafil achieved steady-state levels by day 3 following once daily tadalafil dosing. The 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:




Following figure shows mean supine heart rate at steady-state on day 7:




- For supine heart rate, a greater number of subjects demonstrated mean maximum values (Day 7, 0 to 8 hours postdose) that exceeded the upper limit of the reference range (80 and 100 bpm for supine and standing heart rate, respectively) 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.

Following table summarizes mean supine and standing vital signs (day 7, 0 to 8 hrs):

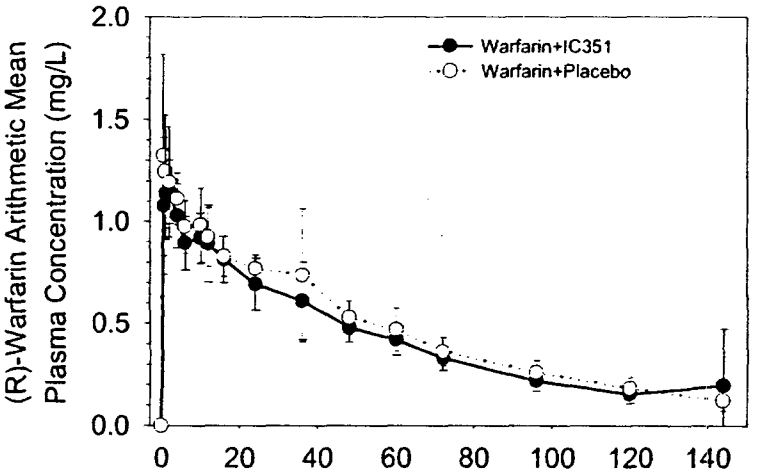
| Treatment | | Supine vital signs | | | Standing vital signs | | |
|---|---|---|---|---|---|---|---|
| | | Heart rate (bpm) | Systolic BP (mmHg) | Diastolic BP (mmHg) | Heart Rate (bpm) | Systolic BP (mmHg) | Diastolic BP (mmHg) |
| Theophylline Placebo & 10 mg IC351 | Mean | 67 (6.5) | 117 (5.3) | 66 (6.1) | 79 (3.3) | 119 (5.9) | 74 (6.5) |
| | Min | | | | | | ) |
| | Max | | | | | | ) |
| Theophylline & 10 mg IC351 | Mean | 74 (6.3) | 122 (5.8) | 70 (6.4) | 88 (4.5) | 121 (7.1) | 75 (6.2) |
| | | | | | | | ) |
| Theophylline & IC351 placebo | Mean | 71 (5.0) | 123 (6.0) | 72 (5.7) | 85 (5.2) | 124 (6.6) | 79 (6.7) |
| | Min | | | | | | |
| | Max | | | | | | |
| Theophylline placebo & IC351 placebo | Mean | 64 (5.6) | 119 (6.2) | 67 (5.7) | 80 (4.8) | 120 (5.1) | 75 (4.4) |
| | Min | | | | | | |
| | Max | | | | | | |

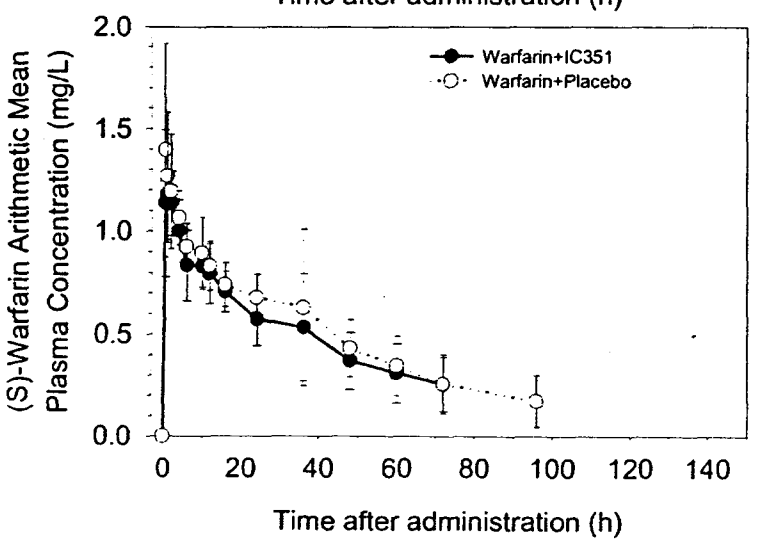
- Increases in mean supine heart rate were larger following theophylline (6 to 7 bpm) than following tadalafil (3 to 4 bpm). When theophylline and tadalafil were given together, the increase in mean supine heart rate (8 to 12 bpm) was larger than when either treatment was given alone. This increase was generally considered additive.

**CYP2C9 Substrate**

*Warfarin* – A Phase I, subject and investigator blind, placebo-controlled, randomized, two-period crossover study was conducted in a healthy male subjects in order to determine the effects of 10 mg tadalafil at steady-state on the pharmacokinetics and pharmacodynamics of a single oral dose 25 mg warfarin. Fourteen subjects entered and 12 subjects completed the study.

- AUC was reduced by 11 and 13% for (R)- and (S)-warfarin, respectively, and for both analytes CL/F and Vz /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.



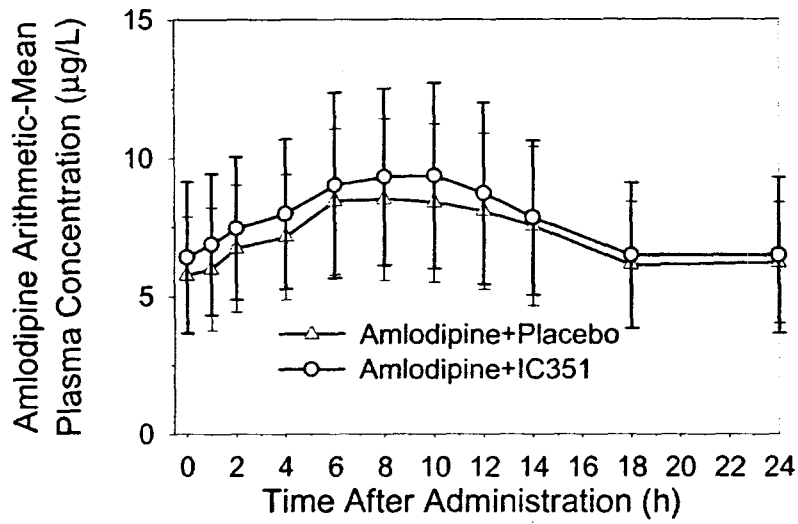



**Amlodipine**

Human liver microsome studies have demonstrated that amlodipine has inhibitory potency towards CYP3A4 and is a weak reversible inhibitor for CYP2D6 and CYP2C9. A Phase I, subject and Investigator blind, placebo-controlled, randomized, two-period crossover study (Study LVAV) was conducted in healthy male and female subjects in order to determine the effects of a single oral dose of tadalafil on the pharmacokinetics and pharmacodynamics of amplodipine at steady-state.

Once daily dosing with 5 mg amlodipine was conducted for a minimum of 14 days prior to 10 mg tadalafil or placebo dosing in Treatment Period 1, until steady-state was reached, and subjects continued on amlodipine therapy until the completion of the study. In the first treatment period, nine subjects were randomized to receive tadalafil and nine subjects were to randomized to receive placebo. After an tadalafil washout period of at least 10 days, subjects received the alternate therapy.

Arithmetic mean plasma concentrations of amlodipine at steady-state in the presence and absence of a single dose of 10 mg tadalafil are presented in the following figure:




Following table shows geometric mean pharmacokinetic parameters of amlodipine

| Parameter | Amlodipine & IC351 | Amlodipine & placebo |
|---|---|---|
| AUC(0-24) (µg*h/L) | 174 (37.8) | 163 (34.2) |
| $C_{max}$ (µg/L) | 9.34 (36.6) | 8.57 (31.3) |
| $t_{max}$[a] (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) (µg*h/L) | 2761 (21.0) |
| $C_{max}$ (µg/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.



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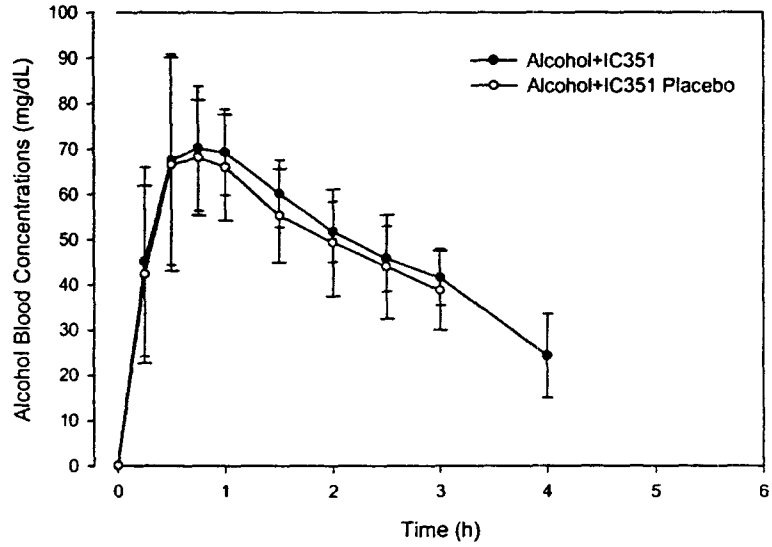
**Alcohol**

There was no significant pharmacokinetic interaction between tadalafil and ethanol. A placebo-controlled four period crossover study was performed in which 10 mg tadalafil, or a placebo tablet, was administered to healthy male subjects 2 hours prior to a single dose of alcohol (0.7 g/kg) or alcohol placebo.

Arithmetic mean blood alcohol concentration-time profiles after dosing with 10 mg tadalafil and alcohol with tadalafil placebo are presented in the following figure:




- Values for $C_{max}$ ranged from [redacted] following administration of alcohol in the presence and absence of tadalafil, respectively. These levels are close to 80 mg/dL, the legal intoxication level in the UK and several states in the USA.

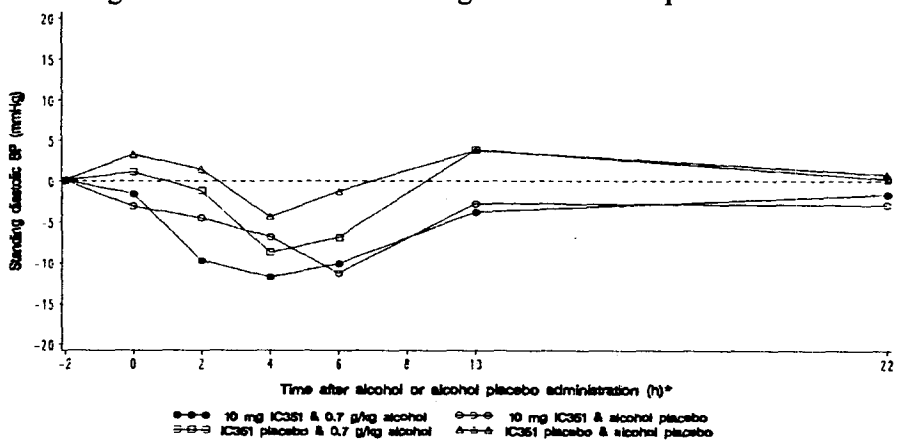
- Geometric means for AUC(0-$t_n$), AUC(0-3) and $C_{max}$ for alcohol were 15%, 2% and 4% higher, respectively, following co-administration with tadalafil compared to with tadalafil placebo. All geometric mean ratios were close to one and the 90% CI for all ratios contained one, and were within 0.8 to 1.25 limits. Median $t_{max}$ 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.

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) |
| $AUC(0\text{-}3)_{norm}$ (g*h/mL) | 225 (12.3) | 221 (9.73) |
| $AUC(0\text{-}t_n)$ (mg*h/dL) | 185 (20.2) | 162 (40.6) |
| $AUC(0\text{-}t_n)_{norm}$ (g*h/dL) | 261 (19.5) | 227 (39.9) |
| $C_{max}$ (mg/dL) | 79.3 (15.1) | 76.6 (19.7) |
| $C_{max,norm}$ (g/dL) | 112 (15.1) | 108 (19.3) |
| $t_{max}$ (h)[a] | 0.750 | 0.750 |
| $C(t_n)$ (mg/dL) | 30.8 (16.1) | 33.8 (15.2) |
| $t_n$ (h) | 3.71 (16.2) | 3.32 (26.0) |

- Impairment of saccadic eye movement parameters (saccadic gain, amplitude or final eye position.) occurred following co-administration of tadalafil with alcohol compared to the administration of either alcohol or tadalafil alone.
- Following co-administration of tadalafil with alcohol, there were trends for greater impairment of some parameters (postural stability and word recognition) compared to the administration of alcohol with tadalafil placebo.
- 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). Following figure shows mean changes from baseline for standing diastolic blood pressure:




- Baseline values were similar for all treatments, however increases in heart rate were greatest following co-administration of tadalafil with alcohol.

- The overall incidence of adverse events (56% vs 25%) was highest following administration of tadalafil with alcohol compared to other combinations.

Another study 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.



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*Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?*

Tadalafil enhances the smooth muscle-relaxant effects of activators of guanylyl cyclase by potently inhibiting PDE5, thereby potentiating the vasodilatory effect of nitric oxide and facilitating the achievement and maintenance of an erection. Thus, interaction of tadalafil with known vasodilators or antihypertensive agents could produce increased vasodilation and cardiovascular changes that may lead to complications with hypotension.

**Nitrates**

- A survival analysis was conducted that compared the maximally tolerated nitroglycerin infusion rate during each of the four treatment arms: multiple dose placebo, single dose 10 mg tadalafil, multiple dose 10 mg tadalafil, and multiple dose 50 mg sildenafil. The distribution of subjects to doses at which they reached the pharmacodynamic endpoint (drop in SBP of =20 mm Hg), by treatment was determined. (See Individual study reviews for details). The percentages of subjects who were able to tolerate the highest dose of nitroglycerin were 36%, 27%, 10% and 9% for multiple dose placebo, single dose 10 mg tadalafil, multiple dose 10 mg tadalafil, and multiple dose 50 mg sildenafil, respectively.

- A similar number of subjects had clinically significant changes in standing systolic and diastolic blood pressure following administration of 0.4 mg sublingual nitroglycerin with 10 mg tadalafil and with 50 mg sildenafil, the frequency of which was generally up to two-fold higher than for nitrate administered with placebo.

- More drug-related adverse events occurred following tadalafil (67%) than for sildenafil (48%), the incidence of adverse events being lowest for placebo (24%).

- The most common drug-related adverse events were myalgia, headache, and back pain, which were more frequent following tadalafil (33, 22, and 9 episodes, respectively) than for sildenafil (13, 16, and 4 episodes, respectively) and placebo (3, 7 and 4 episodes, respectively).

- Tadalafil potentiates the hypotensive effect of organic nitrate in subjects with chronic stable angina. Potentiation of the hypotensive effect was more pronounced for short-acting nitrates than for a chronically administered long-acting nitrate therapy.

**Other 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 $AT_1$-receptor antagonists in hypertensive subjects, based on ambulatory systolic blood pressure. More drug-related adverse effects were observed when angiotensin $AT_1$ 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 ATI receptor antagonist | 25 | 14 | 47.1 | 27.8 |
| Tamsulosin | Similar | | 16.7 | 0.0 |

*include systolic and diastolic

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*Based on BCS principles, in what class is this drug and dosage form? What solubility, permeability and dissolution data support this classification?*

The aqueous solubility of tadalafil is low ——— : however, the compound has been determined to be ——————————— permeability studies. These data established tadalafil as a BCS Class 2 compound. As the market image tablet is an ——————— formulation, an *in vitro/in vivo* correlation analysis was not considered necessary to set production specifications.

Following table shows the solubility data at ———

| Solvent | Amount Dissolved (mg/mL) |
|---|---|
| Water | |
| | |
| | |
| | |
| | |
| | |
| | |
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| | |
| | |

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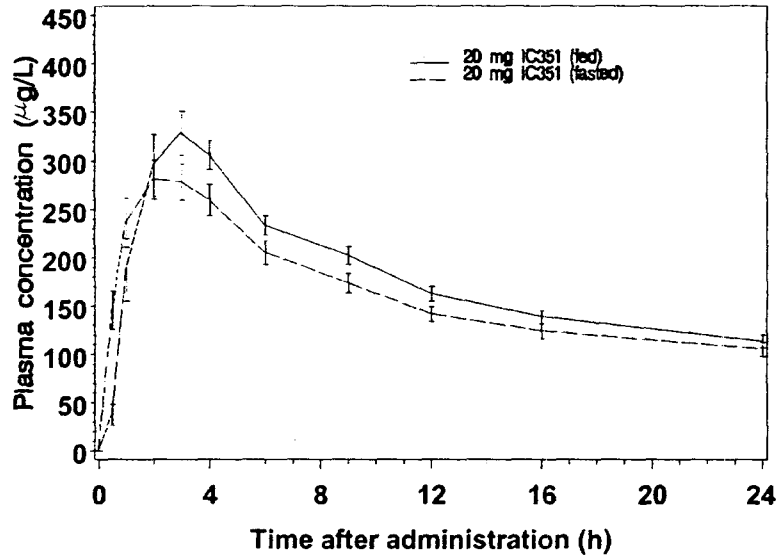
*What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?*

An open-label, two-period crossover study was conducted in 18 healthy male and female subjects in order to compare the pharmacokinetics of tadalafil following a single 20 mg oral dose administered in the fasted state and in the fed state. For dose administration in the fed state, subjects received a high fat, high calorie breakfast within 20 minutes prior to dosing. The meal was ingested at a steady rate over a 15 minute period, such that it was completed within five minutes prior to dosing. The 20 mg market image tablet used in this study was identical to the proposed commercial tablet.

Mean plasma concentration-time profiles for tadalafil following 20 mg single oral doses administered in the fed (high fat) and fasted states are presented in the following figure:




Geometric mean (CV%) pharmacokinetic parameters of tadalafil after oral administration of a single 20 mg dose in the fed (high fat) and fasted states are presented in the table below:

| | Treatment | |
|---|---|---|
| Parameter | 20 mg IC351 (fed) (N=18) | 20 mg IC351 (fasted) (N=18) |
| AUC (µg*h/L) | 6943 (27.8) | 6419 (32.3) |
| AUC(0-$t_n$) (µg*h/L) | 6896 (27.4) | 6372 (31.9) |
| $C_{max}$ (µg/L) | 345 (26.5) | 297 (29.8) |
| $t_{max}$ (h)[a] | 2.50 | 2.00 |
| $t_{1/2}$ (h) | 17.0 (25.5) | 17.3 (24.2) |
| CL/F (L/h) | 2.88 (27.8) | 3.12 (32.3) |
| $V_z$/F (L) | 70.7 (18.6) | 77.6 (20.6) |

- In the presence of food, there was an increase in $C_{max}$ (16%) and AUC (8%) and $t_{max}$ occurred later (0.5 hours) compared with the fasted state.

- The 90% CI for the geometric mean least squares mean ratios were fully contained within the limits of 0.80 to 1.25 and 0.70 to 1.43 for AUC and $C_{max}$, respectively. $T_{max}$ was also similar for both treatments.
- The number of subjects with adverse events and the incidence of adverse events were similar following both treatments.
- Based on these findings, it appears tadalafil can be administered without regard to food.



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*How do the dissolution conditions and specifications assure in vivo performance and quality of the product?*

Following are the Proposed Product Dissolution Specifications:

| | |
|---|---|
| Dosage Form: | Market Image Tablet |
| Strength: | 20 mg |
| Apparatus Type: | USP Dissolution Apparatus |
| Media: | |
| Volume: | 1000 mL |
| Speed of Rotation: | |
| Sampling Time(s): | 5, 10, 20, 30 minutes |
| Brief Description of Dissolution Analytical Method: | The dissolution samples are analyzed by using the |
| Recommended Dissolution Specification: | Not less than (Q) in minutes and not less than (Q) in minutes |

The dissolution media uses a 0.5% concentration and a speed. The level of 0.5% was chosen to target a level of greater solubility for the highest anticipated dose of 20 mg, The level provides at l (USP) the level of o A is not used since pH has no influence on the dissolution of tadalafil and the excipients.

The proposed specification limits for dissolution are not less than (Q = minutes and not less than (Q = at minutes. The minute specification assures that the drug is completely released from the tablet while the minute specification assures that release from the tablet occurs rapidly which is necessary to achieve early onset of action.

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4.5 Analytical

- A high performance liquid chromatography method was used for the determination of tadalafil and IC710 concentration in human plasma.

- Plasma concentrations in the majority of studies were determined with an assay method validated over a concentration range of

- The major metabolite, the methylcatechol glucuronide, was measured in hydrolyzed plasma in three studies using an LC/MS/MS assay method validated over the range 1 to 500 µg/L. As no analytical standard was available for the methylcatechol glucuronide (the glucuronide of IC710), this metabolite cannot be measured directly. Total IC710 in hydrolyzed plasma represents both unconjugated IC710 in plasma as well as IC710 after hydrolysis of existing glucuronide. Hydrolysis of the conjugated products was accomplished by incubating the plasma sample overnight at approximately .

- Dilution of plasma samples up to a concentration of 4000 µg/L was also validated for tadalafil and the methylcatechol glucuronide.

Following table lists individual methods and intra/inter-assay precision and accuracy:

| Method | Precision | Accuracy |
|---|---|---|
| | | |
| | | |
| | | |
| | | |

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

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

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/s/

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Sandip Roy
4/29/02 12:13:06 PM
BIOPHARMACEUTICS

Ameeta Parekh
4/29/02 12:41:29 PM
BIOPHARMACEUTICS
I concur

Individual Study Reviews

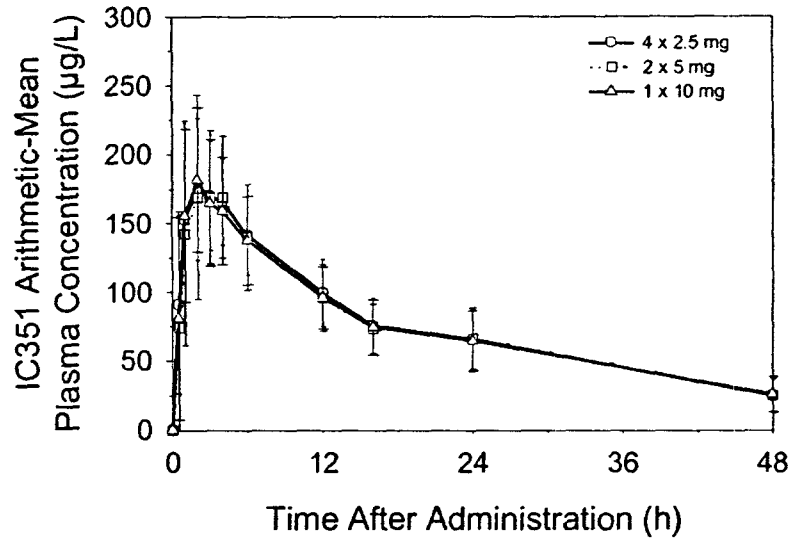
**H6D-EW-LVBX**

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

This study was conducted in two separate parts, one to compare three different tablet strengths of tadalafil at a single oral dose level of 10 mg and another to assess the dose proportionality of tadalafil following single doses of 2.5, 5, 10 and 20 mg. Part A was a single (subject)-blind, three period crossover study in 24 healthy subjects to compare the pharmacokinetics of a single 10 mg dose of tadalafil administered as three tablet strengths (4 x 2.5 mg, 2 x 5 mg and 1 x 10 mg). In Part B, a separate group of 16 subjects was studied over four treatment periods to assess the dose proportionality of tadalafil at single dose levels of 2.5, 5, 10 and 20 mg.

*Part A*

Arithmetic mean plasma concentration-time profiles following dosing of 10 mg tadalafil at each of the three tablet strengths are presented in the following figure:




- Values for $C_{max}$ were similar between tablet strengths, with overall individual values ranging from .

- Median $t_{max}$ was 2 hours for all tablet strengths. Individual $t_{max}$ values were generally between 0.5 and 6 hours.

Following table summarizes geometric mean (CV%) pharmacokinetic parameters of tadalafil following oral administration of a single 10 mg dose as three tablet strengths (4 x 2.5 mg, 2 x 5 mg and 1 x 10mg):

| Parameter | 10 mg IC351 (4 x 2.5 mg tablets) (N=24) | 10 mg IC351 (2 x 5 mg tablets) (N=24) | 10 mg IC351 (1 x 10 mg tablets) (N=24) |
|---|---|---|---|
| AUC (μg*h/L) | 4120 (30.7) | 4071 (32.5) | 4005 (34.2) |
| AUC(0-$t_n$) (μg*h/L) | 4082 (30.4) | 4028 (31.9) | 3968 (33.8) |
| AUC(0-24) (μg*h/L) | 2463 (22.4) | 2396 (26.5) | 2402 (23.3) |
| $C_{max}$ (μg/L) | 190 (23.4) | 196 (28.5) | 184 (24.3) |
| $t_{max}$ (h)[a] | 2.00 | 2.00 | 2.00 |
| $t_{1/2}$ (h) | 18.0 (28.8) | 17.7 (32.0) | 17.6 (27.8) |
| CL/F (L/h) | 2.43 (30.7) | 2.46 (32.5) | 2.50 (34.2) |
| $V_z$/F (L) | 63.0 (23.6) | 62.9 (20.7) | 63.5 (22.7) |



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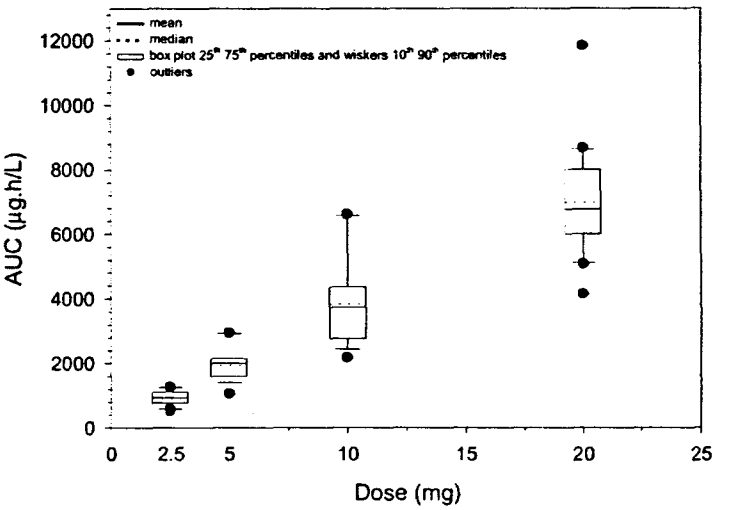
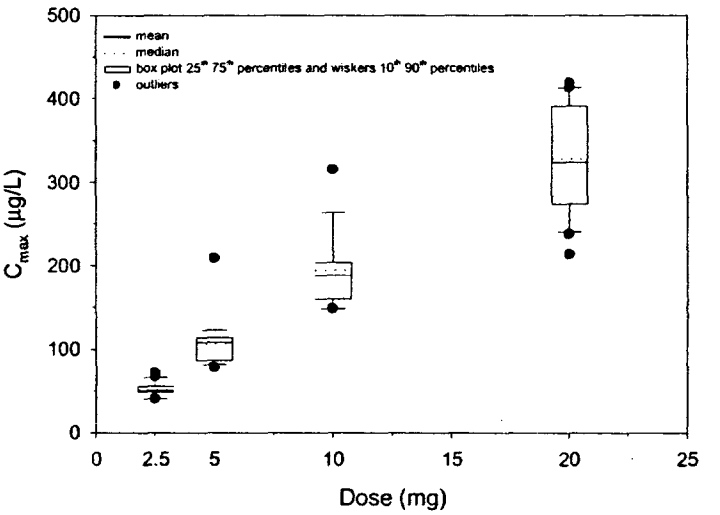
*Part B*

Following figure shows Box and Whisker plots for AUC and $C_{max}$ following single oral administration of 2.5 mg, 5 mg, 10 mg and 20 mg (2 x 10 mg) of tadalafil in Healthy Subjects




- The AUC increased in a dose proportional manner across the 2.5 to 20 mg dose range.

- The estimate β (slope) was close to unity and the 95% confidence intervals for the estimate included one.

- For $C_{max}$ , the estimate of β was less than one and the 95% confidence interval excluded one, indicating $C_{max}$ 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 (µg*h/L) | 900 (27.2) | 1888 (27.5) | 3647 (34.0) | 6809 (24.8) |
| AUC(0-$t_n$) (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) |
| $C_{max}$ (µg/L) | 51.6 (16.1) | 103 (25.0) | 190 (21.7) | 322 (21.2) |
| $t_{max}$ (h)[a] | 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 $t_{max}$ across the dose range (from 1 to 3 hours).
- For $t_{1/2}$, CL/F and $V_z$/F, estimates of β 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.



APPEARS THIS WAY
ON ORIGINAL

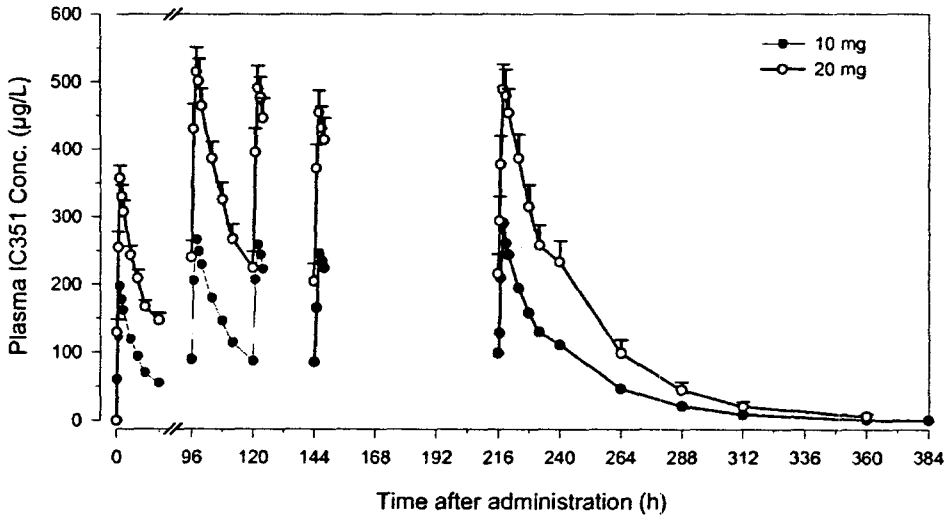
**H6D-EW-LVDK**

**A Study to Evaluate the Multiple Dose Cardiovascular Dynamics and Pharmacokinetics of Tadalafil 10 mg and 20 mg (Market Image Formulation) in Healthy Subjects**

A Phase I, Investigator and subject-blind, placebo-controlled, randomized, parallel design study was conducted in healthy male subjects in order to investigate the haemodynamic effect of multiple doses tadalafil, and to investigate the multiple dose pharmacokinetics of tadalafil and its metabolite, as total IC710 (unconjugated methylcatechol (IC710) plus methylcatechol glucuronide), at dose levels of 10 and 20 mg.

Seventy-five subjects completed the study, 47 subjects in Group A (hemodynamic assessments only) and 28 subjects in Group B (hemodynamic assessments and pharmacokinetic analyses).

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 hydrolyzed plasma (predominantly the methylcatechol glucuronide) were approximately 3-fold higher than single dose values. Following figure shows mean (±SEM) tadalafil concentrations following once-daily administration of 10 and 20 mg doses.




The estimates of accumulation based on $AUC_\tau$ (approximately 1.6-fold for 10 and 20 mg) were comparable to the expected accumulation index of 1.63. The mean values for $t_{1/2}$, CL/F and Vz/F were consistent with single dose values and indicated an absence of auto-induction or auto-inhibition of metabolism.

The steady-state PK parameters of tadalafil following once-daily administration of a 20 mg dose are presented in the table below:

| | Geometric mean (CV%) | | |
|---|---|---|---|
| **Parameter** | **Day 1 (n=15)** | **Day 5 (n=15)** | **Day 10 (n=13)** |
| $AUC_\tau$ (µg*h/L) | 4950 (23.0) | 7692 (31.1) | 7389 (38.2) |
| $C_{max}$ (µg/L) | 352 (24.5) | 514 (26.8) | 481 (31.0) |
| $t_{max}$ (h)[a] | 2.0 (1.0-3.0) | 2.0 (1.0-4.0) | 2.0 (1.0-3.0) |
| $t_{1/2}$ (h) | - | - | 18.7 (40.4) |
| CL/F (L/h) | - | 2.6 (31.1) | 2.71 (38.2) |
| $V_z$/F | | - | 73.1 (22.9) |
| Accumulation Ratio[b] for $AUC_\tau$ | | 1.58 | 1.55 |
| Accumulation Ratio[b] for $C_{max}$ | | 1.49 | 1.41 |

[a] Median (min-max) data.

[b] Geometric LS mean.



APPEARS THIS WAY
ON ORIGINAL

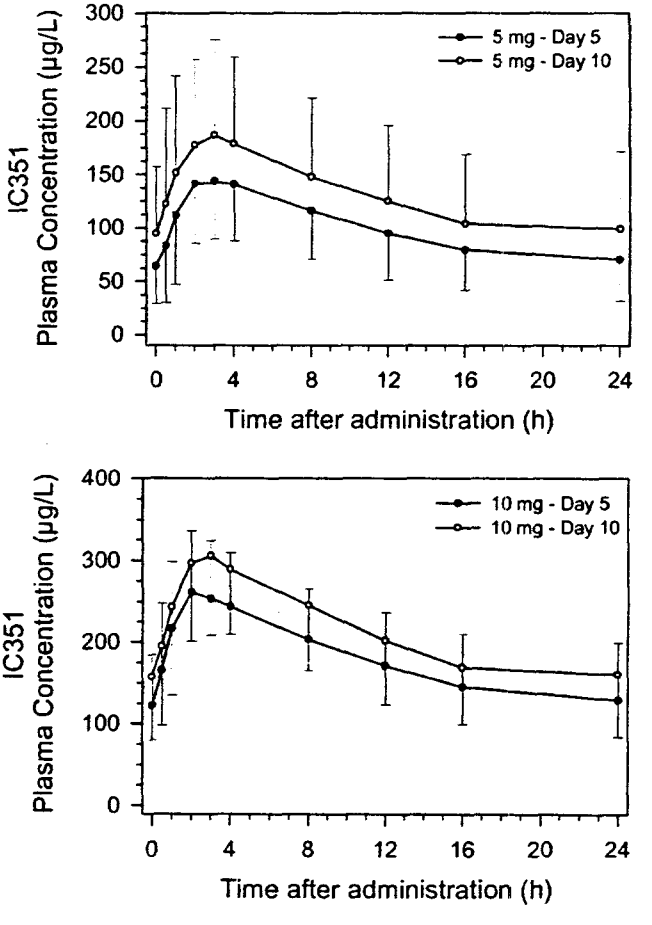
**H6D-EW-LVAU**

**A Study to Evaluate and Compare the Single Dose and Multiple Dose Pharmacokinetics of Tadalafil (5 and 10 mg, Market Image Formulation) and its Methylcatechol Glucuronide Metabolite in Healthy Male Subjects**

A phase I, subject and investigator-blind, placebo-controlled, randomized, two-period parallel design study was conducted in healthy male subjects in order to investigate the safety and tolerability of single and multiple doses of 5 and 10 mg tadalafil, and to investigate the single and multiple dose pharmacokinetics of tadalafil and its methylcatechol glucuronide metabolite as total IC710.

Twelve healthy male subjects first received a 5 mg tablet as a single dose and, after a washout period, received a 5 mg tablet once-daily for 10 days. The second group of 12 subjects received 10 mg tablets in the same manner.

Following figure shows arithmetic mean plasma concentrations of tadalafil following multiple dose administration (Day 5 and Day 10) of 5 mg and 10 mg tadalafil:



Following table shows geometric mean (CV%) pharmacokinetic parameters of tadalafil following single and multiple dose administration of 5 mg tadalafil

| Parameter | Single Dose | Day 5 (Multiple Dose) | Day 10 (Multiple Dose) |
|---|---|---|---|
| AUC (µg*h/L) | 2037 (45.4) | - | - |
| AUC(0-24) (µg*h/L) | 1260 (23.9) | - | - |
| $AUC_\tau$ (µg*h/L) | - | 2155 (48.2) | 2741 (55.2) |
| $C_{max}$ (µg/L) | 90.9 (15.0) | 142 (38.6) | 177 (41.1) |
| $t_{max}$ (h)[a] | 2.00 | 3.00 | 3.00 |
| $t_{1/2}$ (h) | 15.9 (36.0) | - | - |
| CL/F (L/h) | 2.45 (45.4) | 2.32 (48.2) | 1.82 (55.2) |

- Steady state was not achieved with 5 mg tadalafil by day 10. Mean $AUC_\tau$ was 27% higher on Day 10 than on Day 5. Mean $C_{max}$ was 25% higher on Day 10 than on Day 5.

Following table shows geometric mean (CV%) pharmacokinetic parameters of tadalafil following single and multiple dose administration of 10 mg tadalafil

| Parameter | Single Dose | Day 5 (Multiple Dose) | Day 10 (Multiple Dose) |
|---|---|---|---|
| AUC (µg*h/L) | 3871 (46.6) | - | - |
| AUC(0-24) (µg*h/L) | 2314 (27.9) | - | - |
| $AUC_\tau$ (µg*h/L) | - | 4012 (36.9) | 4788 (36.6) |
| $C_{max}$ (µg/L) | 168 (23.2) | 258 (28.0) | 298 (31.3) |
| $t_{max}$ (h)[a] | 2.00 | 2.00 | 3.00 |
| $t_{1/2}$ (h) | 16.6 (31.7) | - | - |
| CL/F (L/h) | 2.58 (46.6) | 2.49 (36.9) | 2.09 (36.6) |

- Steady state was not achieved with 10 mg tadalafil by day 10. Mean $AUC_\tau$ was 19% higher on Day 10 than on Day 5. Mean $C_{max}$ was 15% higher on Day 10 than on Day 5.

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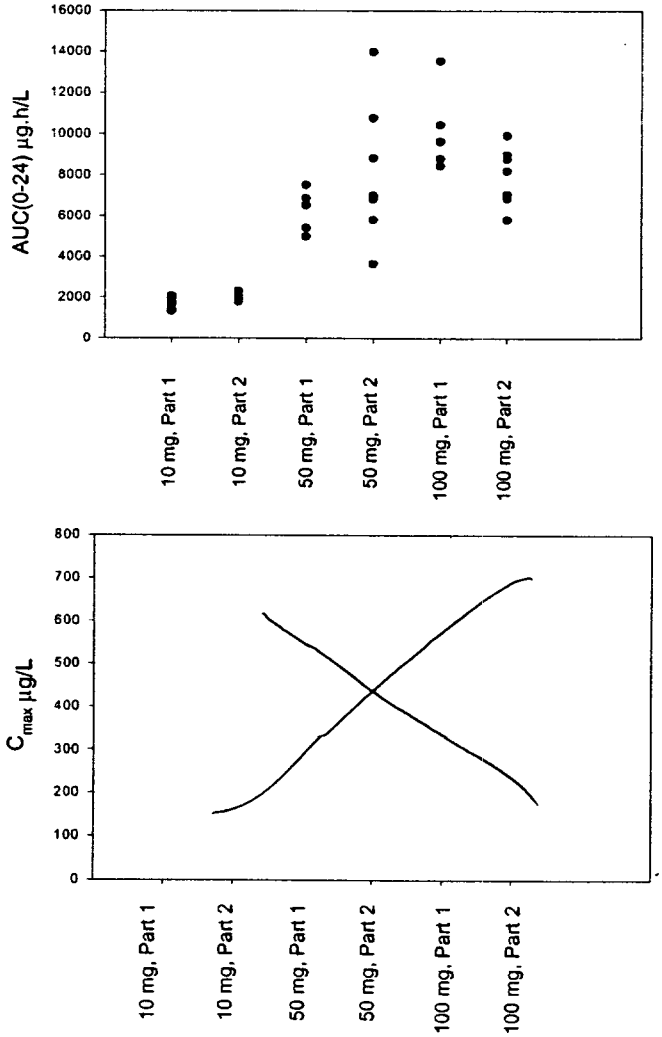
**H6D-MC-LVBH (DSD02)**

**A Phase 1 Study to Assess the Safety, Tolerability, and Pharmacokinetics of Single and Multi-Dose Administration of Tadalafil in Healthy Elderly Male Subjects**

This was a Phase 1, randomized, double-blind, placebo-controlled, sequential dose-escalation study conducted in two parts. The safety, tolerability, and pharmacokinetics of single dose and multi-dose administration of the _____ formulation of Tadalafil to healthy, elderly, male subjects were assessed. Part 1 of the study evaluated single dose administration; Part 2 of the study evaluated once daily administration for seven consecutive days. Tadalafil doses studied consisted of 10 mg, 50 mg, and 100 mg.

Twenty-four subjects received single doses of the following treatments: six 10 mg; six 50 mg; six 100 mg; six placebo. Twenty-eight subjects received multiple doses of the following treatments: six 10 mg; eight 50 mg; six 100 mg; eight placebo.

Following figure shows comparison of AUC following a single oral tadalafil dose on Day 1 of either 10 mg, 50 mg, or 100 mg in Part 1 and Part 2:



- The dose normalized $C_{max}$ and AUC(0-24) values appeared to generally decrease with an increase in dose from 10 mg to 100 mg. This suggests that the increase in $C_{max}$ and AUC(0-24) from 10 mg to 50 mg and 100 mg were less than proportional to dose.

Following table summarizes the pharmacokinetic parameters following single oral Tadalafil doses of 10 mg, 50 mg, and 100 mg (Part 1):

| | Dose | | |
|---|---|---|---|
| **Parameter** | **10 mg (N=6)** | **50 mg (N= 6)** | **100 mg (N=6)** |
| $C_{max}$ (µg/L) | | | |
| Mean | 120 | 332 | 576 |
| Min–Max | | | |
| CV[1] | 17.5 | 12.9 | 21.2 |
| $t_{max}$ (h) | | | |
| Mean | 3.33 | 8.67 | 8.67 |
| Min–Max | | | |
| CV[1] | 31.0 | 94.2 | 90.8 |
| AUC (µg.h/L) | | | |
| Mean | 3228 | 15395 | 24708 |
| Min–Max | | | |
| CV[1] | 27.6 | 18.9 | 35.2 |
| $AUC_{24}$ (µg.h/L) | | | |
| Mean | 1780 | 6299.2 | 10083 |
| Min–Max | | | |
| CV[1] | 15.6 | 15.0 | 18.1 |
| $t_{1/2}$(h) | | | |
| Mean | 19.5 | 22.6 | 23.2 |
| Min–Max | | | |
| CV[1] | 28.2 | 23.9 | 16.5 |

Following table summarizes the pharmacokinetic parameters on Days 1 and 7 following once-daily dosing for seven days– Part 2:

| | Day 1 | | | Day 7 | | |
|---|---|---|---|---|---|---|
| **Parameter** | **10 mg (N=6)** | **50 mg (N=7)** | **100 mg (N=6)** | **10 mg (N=6)** | **50 mg* (N=6)** | **100 mg (N=6)** |
| $C_{max}$(µg/L) | | | | | | |
| Mean | 137 | 434 | 466 | 263.2 | 664 | 723 |
| Min–Max | | | | | | |
| CV[1] | 19.1 | 41.5 | 15.6 | 22.2 | 26.3 | 17.9 |
| $t_{max}$(h) | | | | | | |
| Mean | 2.67 | 7.14 | 5.33 | 2.50 | 4.00 | 3.00 |
| Min–Max | | | | | | |
| CV[1] | 38.7 | 106 | 38.7 | 49.0 | 22.3 | 36.5 |
| AUC(0-24) (µg.h/L) | | | | | | |
| Mean | 2047 | 8119 | 8295 | 3999 | 11935 | 12530 |
| Min–Max | | | | | | |
| CV[1] | 10.2 | 42.2 | 14.3 | 22.5 | 28.0 | 15.7 |
| Accumulation ratio AUC ($R_{A1}$) | | | | | | |
| Mean | | | | 1.95 | 1.74 | 1.52 |
| Min–Max | | | | 1 | | 8 |
| CV[1] | | | | 17.9 | 22.3 | 17.2 |
| Accumulation ratio $C_{max}$ ($R_{A2}$) | | | | | | |
| Mean | | | | 1.96 | 1.81 | 1.59 |
| Min–Max | | | | | | |
| CV[1] | | | | 20.9 | 25.6 | 25.1 |
| $t_{1/2}$(h) | | | | | | |
| Mean | | | | 22.5 | 27.4 | 24.3 |
| Min–Max | | | | | | |
| CV[1] | | | | 27.3 | 16.0 | 20.9 |

- The average accumulation for both $C_{max}$ and AUC increased by approximately 1.9-fold following 10 mg once daily dosing, 1.8-fold following 50 mg once daily dosing, and 1.5-fold following 100 mg once daily dosing.

- Tadalafil apparently was extensively distributed within the body as the apparent volume of distribution following the distribution phase and at steady-state were larger than body water (approximately 42 L).

- The elimination half-life of the ———— formulation of tadalafil was approximately 23 hours following both the single and the last dose following once daily dosing over the 10 mg to 100 mg dose range.

Following table summarizes number and percentage of subjects who experienced the most commonly reported adverse events – Part 1:

| | Part 1 - Single Dose | | | | |
|---|---|---|---|---|---|
| **Variable** | **Placebo** N = 6 | **IC351 10 mg** N = 6 | **IC351 50 mg** N = 6 | **IC351 100 mg** N = 6 | **ALL IC351** N = 18 |
| **Subjects with Events** | 3 (50.0) | 6 (100.) | 6 (100) | 6 (100) | 18 (100) |
| **Body as a Whole** | 1 (16.7) | 4 (66.7) | 2 (33.3) | 5 (83.3) | 11 (61.1) |
| **Headache** | 1 (16.7) | 3 (50.0) | 1 (16.7) | 3 (50.0) | 7 (38.9) |
| **Back Pain** | 0 | 0 | 1 (16.7) | 4 (66.7%) | 5 (27.8) |
| **Musculoskeletal** | 0 | 3 (50.0) | 3 (50.0) | 4 (66.7) | 10 (55.6) |
| **Myalgia** | 0 | 3 (50.0) | 3 (50.0) | 4 (66.7) | 10 (55.6) |

Following table summarizes number and percentage of subjects who experienced the most commonly reported adverse events – Part 2:

| | Part 2 - Multiple Dose | | | | |
|---|---|---|---|---|---|
| **Variable** | **Placebo** N = 8 | **IC351 10 mg** N = 6 | **IC351 50 mg** N = 8 | **IC351 100 mg** N= 6 | **ALL IC351** N = 20 |
| **Subjects with Events** | 8 (100) | 6 (100) | 7 (87.5) | 6 (100.0) | 19 (95.0) |
| **Body as a Whole** | 4 (50.0) | 3 (50.0) | 6 (75.0) | 4 (66.7) | 13 (65.0) |
| **Headache** | 2 (25.0) | 3 (50.0) | 4 (50.0) | 2 (33.3) | 9 (45.0) |
| **Back Pain** | 1 (12.5) | 0 | 2 (25.0) | 2 (33.3) | 4 (20.0) |
| **Musculoskeletal** | 2 (25.0) | 5 (83.3)) | 3 (37.5) | 6 (100.0) | 14 (70.0) |
| **Myalgia** | 2 (25.0) | 4 (66.7) | 3 (37.5) | 6 (100.0) | 11 (55.0) |

- Following single dose administration, adverse events were reported for all subjects in the 10 mg, 50 mg, and 100 mg tadalafil groups, and for three (50.0%) subjects in the placebo group.

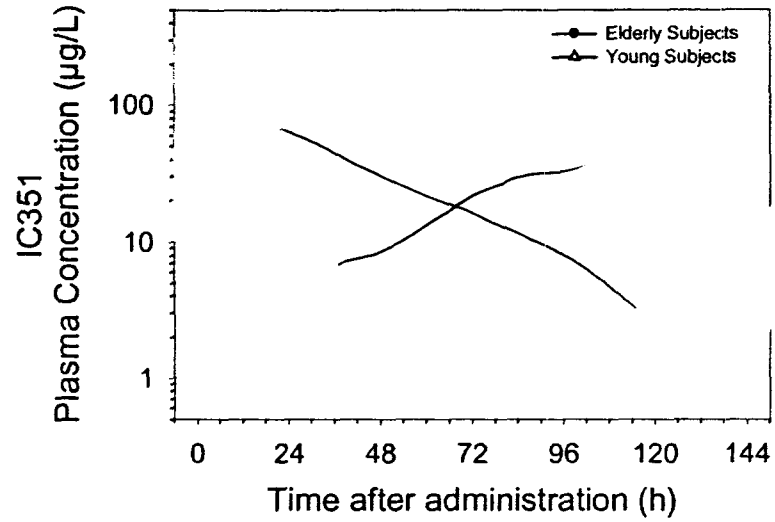
- Upon multiple dosing, adverse events were reported for six (100%) subjects in the 10 mg group, seven (88%) subjects in the 50 mg group, six (100.0%) subjects in the 100 mg group, and eight (100%) subjects in the placebo group.

- The most commonly reported treatment-related adverse events in both Part 1 and Part 2 were headache, back pain, and myalgia.

**H6D-EW-LVBW(a)**

**An Open Study to Compare the Pharmacokinetics after a Single Oral Dose of Tadalafil (LY450190) Administration in Young and Elderly Healthy Male Subjects**

An open-label, parallel group study was conducted in 12 elderly and 12 young male subjects in order to study the effect of age on the pharmacokinetics of tadalafil following a single 10 mg oral dose, and to further assess the safety and tolerability of tadalafil. Following figure shows plasma concentration-time profiles following a 10 mg single oral dose to 12 elderly subjects or 12 young subjects.




The following table shows geometric mean pharmacokinetic parameters after oral administration of a single 10 mg dose in elderly and young Subjects:

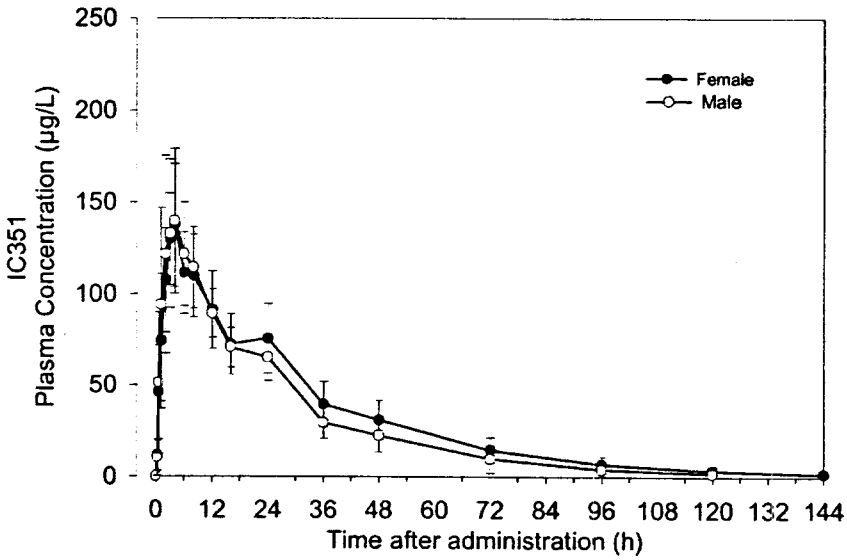
| Parameter | Group | |
|---|---|---|
| | Elderly subjects (N=12) | Young subjects (N=12) |
| AUC (µg*h/L) | 4881 (31.7) | 3896 (42.6) |
| $AUC_{norm}$ (kg*h/L) | 37.6 (33.3) | 30.2 (48.4) |
| AUC(0-tn) (µg*h/L) | 4775 (29.7) | 3861 (42.2) |
| $AUC(0\text{-}tn)_{norm}$ (kg*h/L) | 36.7 (31.4) | 30.0 (48.0) |
| AUC (0-24) (µg*h/L) | 2552 (18.6) | 2388 (27.2) |
| $AUC(0\text{-}24)_{norm}$ (kg*h/L) | 19.6 (14.1) | 18.5 (34.3) |
| $C_{max}$ (µg/L) | 196 (26.9) | 183 (25.5) |
| $C_{max,norm}$ (kg/L) | 1.51 (19.9) | 1.42 (31.6) |
| $t_{max}$ (h)[a] | 2.00 | 2.50 |
| $t_{1/2}$ (h) | 21.6 (39.0) | 16.9 (29.1) |
| CL/F (L/h) | 2.05 (31.7) | 2.57 (42.6) |
| CL/F (L/h/kg) | 0.0266 (33.3) | 0.0331 (48.4) |
| $V_z$/F (L) | 63.9 (25.5) | 62.5 (17.3) |
| $V_z$/F (L/kg) | 0.830 (16.4) | 0.806 (25.5) |

- Apparent clearance was reduced by approximately 20% in the elderly subjects. 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.
- As $C_{max}$, $t_{max}$ and AUC(0-24) were slightly higher in elderly group compared to the younger subjects, this suggests that the rate and extent of drug absorption within this period were not much different between the two groups.
- The major difference in the concentration-time profiles was in terms of the terminal elimination half-life, the mean half-life in the elderly group was approximately 5 hours longer than that of the young group.
- The increase in AUC in the elderly group was not considered to be clinically significant, therefore a change in dose is not warranted.
- Both 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.

**H6D-EW-LVAD**

**A Study to Examine the Safety, Tolerance and Pharmacokinetics of Single and Multiple Doses of LY450190 (Tadalafil) in Healthy Male and Female Subjects**

An open-label, parallel group study was conducted in healthy male and female subjects to investigate the safety, tolerability and pharmacokinetics of tadalafil. All subjects were administered a single oral dose of 10 mg and, following a washout period of 7 days, 10 mg once-daily for 10 consecutive days. Twenty-four subjects (12 female, 12 male) completed the study as planned. Six of the female subjects were postmenopausal and the other six female subjects were surgically sterile. Following figure shows mean plasma concentration vs. time profiles following oral administration of a single 10 mg dose to female and male subjects:

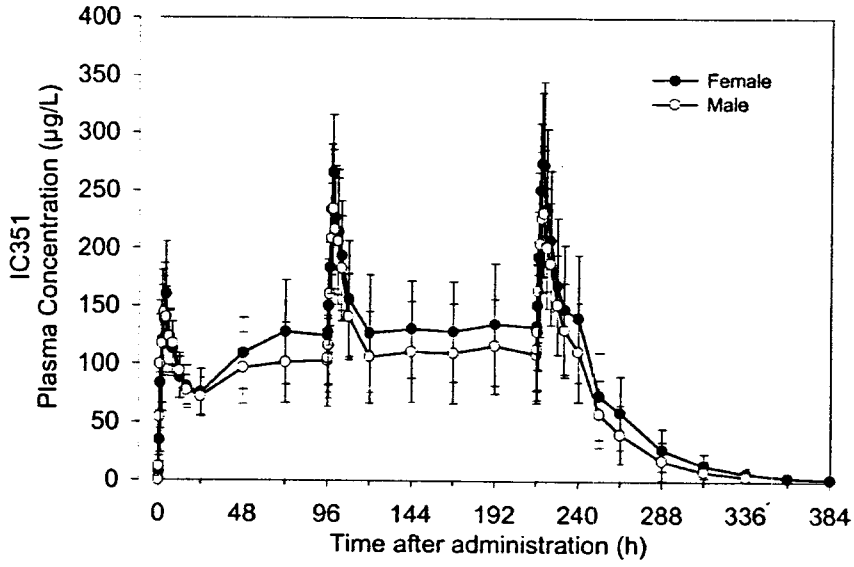



The mean AUC values for female and male subjects show a slight difference (4097 and 3565 µg*h/L, respectively). However, the dose and body weight normalized values were similar (26.2 and 26.4 kg*h/L, respectively). The mean values determined for AUC (0-24) were similar (2136 and 2149 µg*h/L, respectively) which indicates that the higher AUC values for female subjects were due to a difference in the elimination phase between genders. A small difference was observed between the mean $t_{½}$ values for female and male subjects (19.8 and 16.6 hours, respectively). The mean half-life in the females was approximately 3 hours longer than that in males.

Following table shows the geometric mean pharmacokinetic parameters following oral administration of a single 10 mg dose (Day 1 and Day 8) to female and male subjects:

| Parameters | Females | Males | Females | Males |
|---|---|---|---|---|
| | Single Dose Day 1 (N=12) | Single Dose Day 1 (N=12) | Multiple Dose Day 8 (N=12) | Multiple Dose Day 8 (N=12) |
| AUC (µg*h/L) | 4097 (28.2) | 3565 (23.1) | - | - |
| $AUC_{norm}$ (kg*h/L) | 26.2 (32.9) | 26.4 (29.3) | - | - |
| $AUC(t_n\text{-}\infty)$ (%) | 1.03 (72.7) | 0.700 (62.3) | - | - |
| AUC(0-24) (µg*h/L)[a] | 2136 (18.5) | 2149 (17.9) | 2225[b] (19.9) | 2249[b] (16.8) |
| $AUC(0\text{-}24)_{norm}$ (kg*h/L)[a] | 13.7 (18.8) | 15.9 (19.7) | 14.2[b] (16.6) | 16.7[b] (21.3) |
| $C_{max}$ (µg/L) | 140 (21.0) | 142 (26.5) | 164 (26.9) | 149 (19.6) |
| $C_{max,norm}$ (kg/L) | 0.895 (17.4) | 1.05 (26.7) | 1.05 (19.6) | 1.11 (25.8) |
| $t_{max}$ (h)[c] | 3.51 | 3.50 | 4.00 | 3.03 |
| $t_{½}$ (h) | 19.8 (26.1) | 16.6 (21.0) | - | - |
| CL/F (L/h) | 2.44 (28.2) | 2.81 (23.1) | - | - |
| CL/F (L/h/kg) | 0.0382 (32.9) | 0.0379 (29.3) | - | - |
| $V_z$/F (L) | 69.8 (19.3) | 67.2 (16.5) | - | - |
| $V_z$/F (L/kg) | 1.09 (14.5) | 0.907 (15.9) | - | - |

Following figure shows mean plasma concentration vs. time profiles (mean ± SD) following a multiple dose regimen of 10 mg given once-daily for 10 days to female and male subjects:



Following table shows geometric mean pharmacokinetic parameters following oral administration of multiple 10 mg doses (Day 12 and Day 17) to female and male subjects.

| Parameters | Females | Males | Females | Males |
|---|---|---|---|---|
| | Multiple Dose Day 12 (N=12) | Multiple Dose Day 12 (N=12) | Multiple Dose Day 17 (N=12) | Multiple Dose Day 17 (N=12) |
| $AUC_{\tau,ss}$(µg*h/L) | 3927[a] (27.7) | 3534[a] (28.6) | 4184 (33.1) | 3633 (29.5) |
| $AUC_{\tau,ss,norm}$ (kg*h/L) | 25.1[a] (31.4) | 26.3[a] (33.1) | 26.8 (37.2) | 27.0 (35.4) |
| $C_{max,ss}$ (µg/L) | 265 (19.4) | 237 (20.3) | 277 (26.0) | 232 (26.6) |
| $C_{max,ss,norm}$ (kg/L) | 1.70 (19.6) | 1.76 (25.9) | 1.77 (28.4) | 1.72 (34.4) |
| $C_{min,ss}$ (µg/L)[c] | 116 (42.4) | 95.5 (42.5) | 121 (49.2) | 102 (39.1) |
| $C_{av,ss}$ (µg/L) | 164 (27.7) | 147 (28.6) | 174 (33.1) | 151 (29.5) |
| $t_{max,ss}$ (h)[b] | 3.00 | 3.00 | 3.02 | 4.00 |
| $t_{½}$ (h) | - | - | 20.3 (25.5) | 17.8 (27.4) |
| $CL_{ss}/F$ (L/h) | 2.55 (27.7) | 2.83 (28.6) | 2.39 (33.1) | 2.75 (29.5) |
| $CL_{ss}/F$ (L/h/kg) | 0.0398 (31.4) | 0.0381 (33.1) | 0.0373 (37.2) | 0.0371 (35.4) |
| $V_{z,ss}/F$ (L) | - | - | 69.9 (25.4) | 70.6 (17.1) |
| $V_{z,ss}/F$ (L/kg) | - | - | 1.09 (23.1) | 0.950 (14.4) |

Following multiple dose administrations, there was moderate accumulation as evident from the steady-state median accumulation ratios for $C_{max}$ and $AUC_{\tau}$ (Day 17 vs. Day 8). The values of $C_{max}$ were approximately 70% and 80% greater on Days 12 and 17, respectively, compared to Day 8 and $AUC_{\tau}$ was approximately 80% and 90% greater on Days 12 and 17, respectively, compared to Day 8 for females. The values of $C_{max}$ and $AUC_{\tau}$ were approximately 60% greater on Days12 and 17 compared to Day 8 for males. The difference in $t_{½}$ observed after single dose administration is also seen following the final multiple dose (Day 17), the mean values being 20.3 hours for females and 17.8 hours for male.

**H6D-EW-LVAK**

**Comparative Study on the Safety, Tolerability and Pharmacokinetics of Tadalafil, Following Single Oral Dose Administration in Healthy Subjects and in Patients with Very Mild, Mild, Moderate and Severe Liver Impairment**

An open-label, parallel group study was conducted in 8 healthy subjects and 25 patients with varying degrees of hepatic impairment (eight with very mild, mild and moderate impairment, one with severe impairment). The study compared the pharmacokinetics of tadalafil in these populations, following a single oral 10 mg dose, and further assessed the safety and tolerability of tadalafil. Following table lists the geometric mean pharmacokinetic parameters after oral administration of a single 10 mg dose in healthy subjects and patients with hepatic impairment:

| | Group | | | | |
|---|---|---|---|---|---|
| Parameter | Healthy subjects (N=8) | Patients with very mild hepatic impairment (N=8) | Patients with mild hepatic impairment (N=8) | Patients with moderate hepatic impairment (N=8) | Patients with severe hepatic impairment [a] (N=1) |
| AUC (µg*h/L) | 5823 (74.4) | 3961 (34.3) | 5760 (51.7) | 4049 (55.5) | 2260 |
| AUC (0-24) (µg*h/L) | 2591 (36.0) | 1902 (12.9) | 2044 (20.0) | 1348 (37.7) | 1065 |
| $C_{max}$ (µg/L) | 180 (38.1) | 133 (20.8) | 146 (22.8) | 101 (39.4) | 63.9 |
| $t_{max}$ (h)[b] | 2.50 | 3.01 | 2.00 | 2.50 | 3.00 |
| $t_{1/2}$ (h) | 24.2 (52.6) | 24.7 (42.6) | 34.9 (48.4) | 37.8 (62.0) | 23.3 |
| CL/F (L/h) | 1.72 (74.4) | 2.52 (34.3) | 1.74 (51.7) | 2.47 (55.5) | 4.42 |
| $V_z$/F (L) | 59.9 (30.0) | 90.1 (19.3) | 87.5 (24.9) | 135 (55.0) | 149 |
| $V_z$/F (L/kg) | 0.841 (34.6) | 1.10 (20.5) | 1.20 (28.9) | 1.61 (55.1) | 2.16 |
| MRT (h) | 37.1 (54.6) | 35.8 (40.7) | 51.8 (45.3) | 55.2 (59.4) | 36.1 |

[b]Median (min – max)

- 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. The AUC value for the single patient with severe hepatic impairment was comparable to the lowest individual values for the other groups.
- There was no consistent trend in apparent oral clearance (CL/F) across severity of hepatic impairment.

- The apparent volume of distribution (Vz /F) appeared to increase with increasing severity of impairment. An approximately 2-fold increase in Vz /F compared to the geometric mean value for healthy subjects was found for the moderately impaired group.
- Terminal half-life values tended to be prolonged and more variable across individuals with hepatic impairment.



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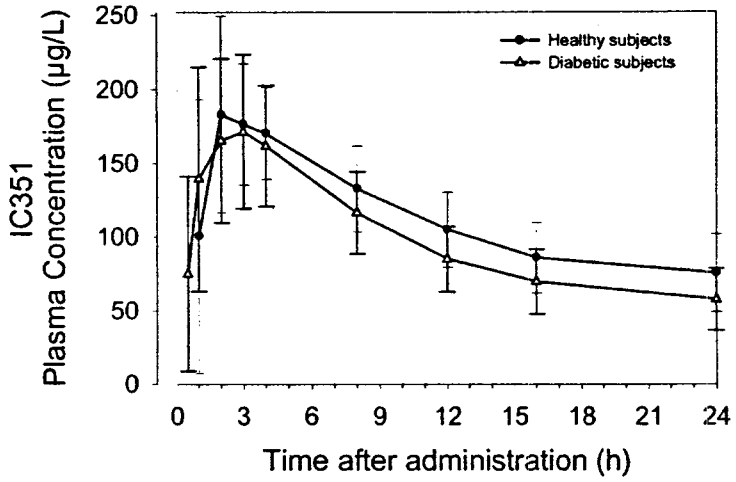
**H6D-EW-LVAS**

**An Open Study to Compare the Pharmacokinetics After a Single Oral Dose of Tadalafil Administration in Diabetics and Healthy Subjects**

This was an open-label, single centre, parallel group study conducted to evaluate the pharmacokinetics, safety and tolerability of tadalafil in diabetic and healthy subjects following a single 10 mg tablet.

Arithmetic mean (±SD) plasma concentration-time profiles (linear scale) of tadalafil after oral administration of a single 10 mg dose in diabetic subjects (n=12) and healthy subjects (n=12) are presented in the following figure:




Geometric mean (CV%) pharmacokinetic parameters of tadalafil after oral administration of a single 10 mg dose in diabetic and healthy subjects are presented in table below:

| | Group | |
|---|---|---|
| Parameter | Diabetic subjects (N=12) | Healthy subjects (N=12) |
| AUC (µg*h/L) | 3458 (38.2) | 4249 (36.2) |
| $AUC_{norm}$ (kg*h/L) | 25.5 (40.8) | 31.4 (33.3) |
| $AUC(0\text{-}t_n)$ (µg*h/L) | 3437 (38.2) | 4220 (35.9) |
| $AUC(0\text{-}t_n)_{norm}$ (kg*h/L) | 25.3 (40.8) | 31.2 (33.1) |
| AUC(0-24) (µg*h/L) | 2258 (27.2) | 2575 (23.0) |
| $AUC(0\text{-}24)_{norm}$ (kg*h/L) | 16.6 (27.3) | 19.0 (21.1) |
| $C_{max}$ (µg/L) | 184 (27.1) | 193 (21.6) |
| $C_{max,\ norm}$ (kg/L) | 1.36 (26.5) | 1.43 (28.3) |
| $t_{max}$ (h)[a] | 3.00 | 2.00 |
| $t_{lag}$ (h)[a] | 0.00 | 0.25 |
| $t_{½}$ (h) | 13.8 (33.2) | 17.1 (26.8) |
| CL/F (L/h) | 2.89 (38.2) | 2.35 (36.2) |
| $V_z$/F (L) | 57.4 (18.2) | 58.2 (23.3) |

- Mean values for $C_{max}$ and AUC(0-24) were 5 and 11% lower in diabetic subjects compared to healthy subjects
- Mean values for AUC and AUC(0-tn) were approximately 19% lower when tadalafil was administered to diabetic subjects and the 90% CI for the ratios fell outside the lower limit of —
- Mean CL/F was approximately 23% higher in diabetic subjects, reflecting the reduced systemic exposure (AUC) in this group. Mean Vz/F was similar for the two study populations.
- The mean terminal half-life was approximately 3 hours shorter in diabetic subjects compared to healthy subjects.
- Since AUC(0-24) was approximately 11% lower for diabetic subjects and mean AUC was approximately 19% lower for the diabetic subjects than for healthy subjects, it appears the reduced systemic exposure in diabetic subjects is due to a difference in the terminal elimination half-life.



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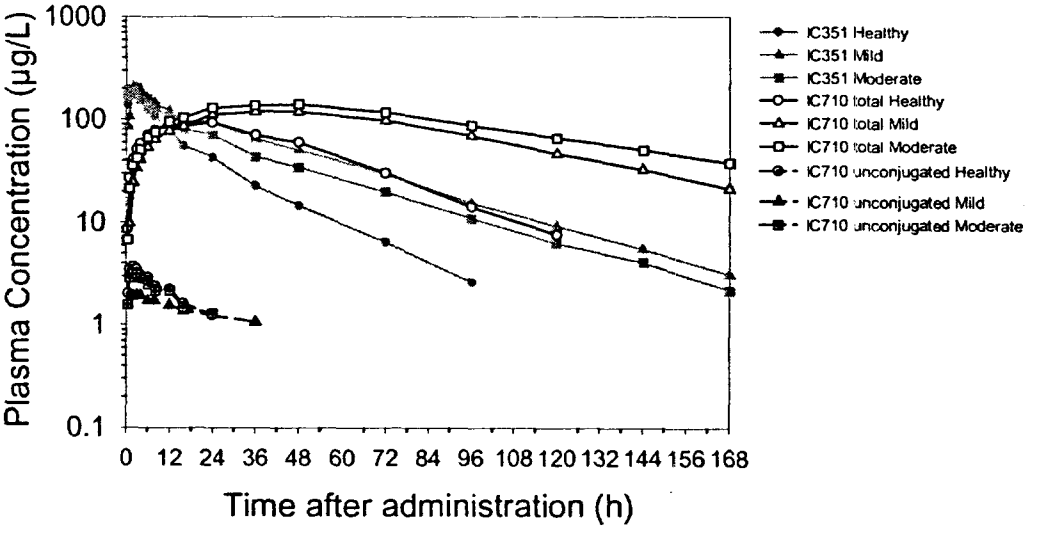
**H6D-EW-LVAJ**

**Comparative Study on the Pharmacokinetics, Safety and Tolerability of IC351, Following a Single Oral Dose in Patients with Mild, Moderate or Severe Renal Dysfunction and Healthy Subjects**

A Phase I, open-label study was conducted to investigate the effects of renal impairment on the pharmacokinetics of tadalafil and its methylcatechol glucuronide metabolite following single oral doses of 10 and 5 mg tadalafil. A total of 12 healthy subjects (8 receiving 10 mg, 4 receiving 5 mg), 8 patients with mild renal impairment (5 receiving 10 mg, 3 receiving 5 mg) and 12 patients with moderate renal impairment (6 receiving 10 mg, 6 receiving 5 mg) were dosed. No patient with severe renal impairment received either dose level of tadalafil. Plasma obtained during the study was analysed for tadalafil (IC351) and unconjugated methylcatechol (IC710). Total methylcatechol (total IC710) was also analyzed in hydrolysed plasma, because there is no analytical standard for conjugated (glucuronidated) methylcatechol.

Following figure shows mean plasma concentrations of tadalafil (IC351) and IC710 (Total and Unconjugated) in healthy subjects and in patients with mild and moderate renal impairment following administration of a single 10 mg dose:




- Mean tadalafil AUC increased by approximately 2- fold and $C_{max}$ by approximately 1.2-fold in patients with mild and moderate renal impairment. The range in $t_{max}$ values was similar for all groups, median values being in the range of 1 to 2 hours. Apparent oral clearance (CL/F) was reduced in the renally impaired subjects, which resulted in a longer apparent $t_{1/2}$.
- Mean exposure (AUC) of total IC710 increased in patients with moderate and mild renal impairment by approximately 3.6 and 2.6 fold, respectively. Total IC710 $C_{max}$ increased by approximately 1.6- and 1.3- fold for patients with moderate and mild renal impairment, respectively. Thus, the total IC710 data suggests that apparent

renal clearance of the metabolite decreases with renal impairment, which results in a later $t_{max}$, a longer apparent terminal half-life and a larger AUC.

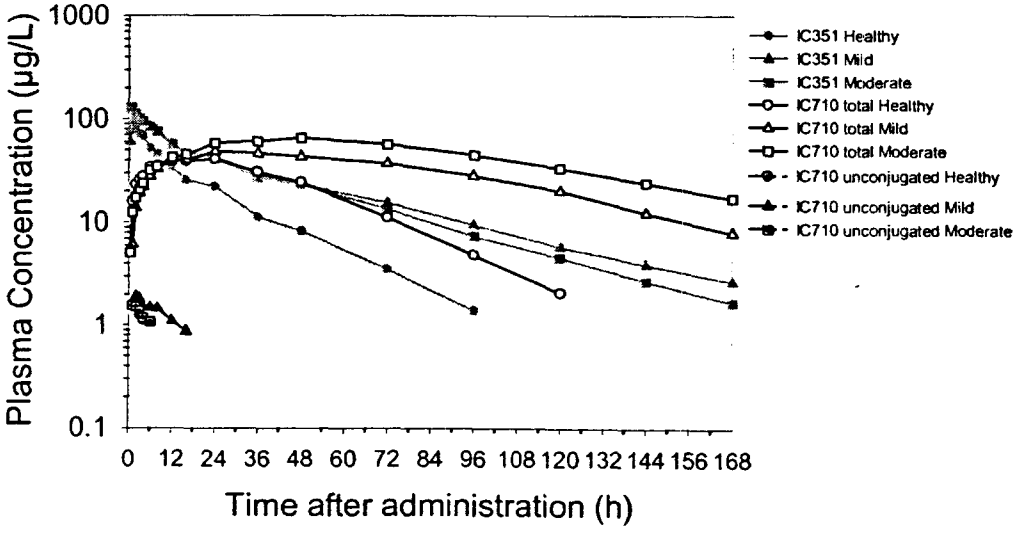
Geometric mean (CV%) pharmacokinetic parameters of tadalafil after oral administration of a single 10 mg dose in healthy subjects and patients with renal impairment are shown in the following table:

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

Following table summarizes geometric mean (CV%) pharmacokinetic parameters of total IC710 (methylcatechol glucuronide) after oral administration of a single 10 mg dose in healthy subjects and patients with renal impairment:

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

Following figure shows mean plasma concentrations of tadalafil (IC351) and IC710 (total and unconjugated) in healthy subjects and in patients with mild and moderate renal impairment following administration of a single 5 mg dose:



- Mean tadalafil AUC increased by approximately 2- fold and $C_{max}$ by approximately 1.3- fold in patients with mild and moderate renal impairment compared to healthy subjects. Apparent oral clearance (CL/F) was reduced in the renally impaired subjects, which resulted in a longer apparent $t_{1/2}$.
- Mean exposure (AUC) for total IC710 appeared to increase in relation to renal impairment, with the more pronounced effect being in patients with moderate renal impairment. The parameter AUC was approximately 3.6- fold and 2.2- fold higher in moderate and mild renally impaired subjects. The parameter $C_{max}$ also increased with the degree of renal impairment, being approximately 1.6- and 1.3- fold higher for patients with moderate and mild renal impairment, respectively. The mean terminal elimination half-life of total IC710 was longer in the renally impaired patients, being approximately 51 and 31 hours in moderate and mild renal impaired subjects, respectively. These results are consistent with a reduction in the apparent renal clearance of total IC710.

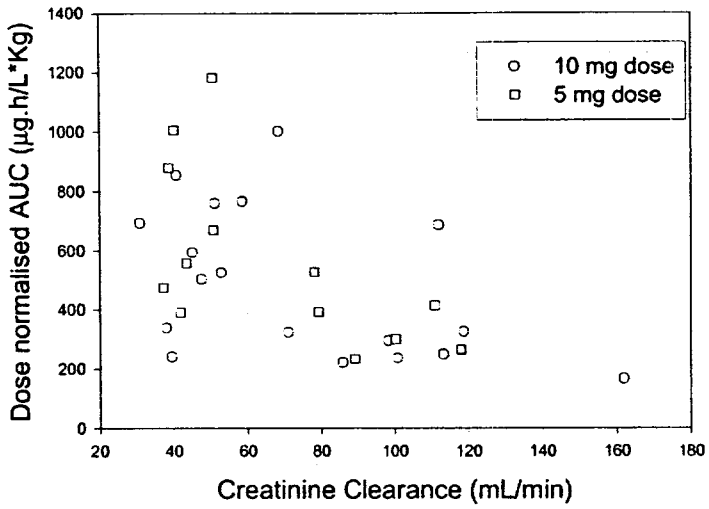
Geometric mean (CV%) pharmacokinetic parameters of tadalafil after oral administration of a single 5 mg dose in healthy subjects and patients with renal impairment are presented in the table below:

| | Group | | |
|---|---|---|---|
| Parameter | Healthy subjects (N=4) | Mild renal impairment (N=3) | Moderate renal impairment (N=6) |
| AUC (µg*h/L) | 1472 (25.1) | 3119 (62.3) | 3135 (37.5) |
| AUC(0-24) (µg*h/L) | 966 (13.7) | 1471 (19.4) | 1555 (16.1) |
| $C_{max}$ (µg/L) | 101 (31.2) | 111 (17.4) | 136 (13.2) |
| $t_{max}$ (h)[a] | 1.00 | 2.00 | 0.500 |
| $t_{1/2}$ (h) | 18 (18.3) | 25 (66.9) | 26 (41.7) |
| CL/F (L/h) | 3.40 (25.1) | 1.60 (62.3) | 1.59 (37.5) |
| $V_z$/F (L) | 87.1 (11.3) | 57.6 (22.0) | 59.9 (25.3) |

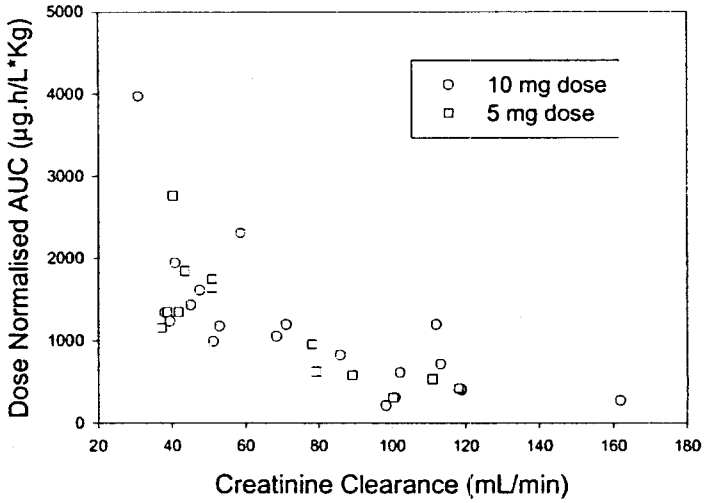
Following table summarizes geometric mean (CV%) pharmacokinetic parameters of total IC710 (methylcatechol glucuronide) after oral administration of a single 5 mg dose in healthy subjects and patients with renal impairment:

| | Group | | |
|---|---|---|---|
| Parameter | Healthy subjects (N=4) | Mild renal impairment (N=3) | Moderate renal impairment (N=6) |
| AUC (µg*h/L) | 2238 (29.3) | 4955 (51.3) | 8123 (32.1) |
| $C_{max}$ (µg/L) | 41.3 (31.0) | 53.3 (7.97) | 65.7 (25.5) |
| $t_{max}$ (h)[a] | 20.0 | 24.0 | 42.0 |
| $t_{1/2}$ (h) | 20 (23.9) | 31 (42.8) | 51 (12.8) |

Following figure shows the plot of creatinine clearance versus dose normalized AUC for tadalafil:




Following figure shows the plot of creatinine clearance versus dose normalized AUC for total methylcatechol (total IC710):




- AUC range for tadalafil was larger at creatinine clearances of less than approximately 70 mL/min. For total IC710, a nonlinear association between individual dose normalized AUC values and creatinine clearance was apparent, with AUC increasing as creatinine clearance decreased.
- The 10 mg dose of tadalafil was reasonably well tolerated in healthy subjects and subjects with mild renal impairment. In subjects with moderate renal impairment, however, there was an increased frequency of pain and myalgia. The 5 mg dose was well tolerated in all groups. 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.



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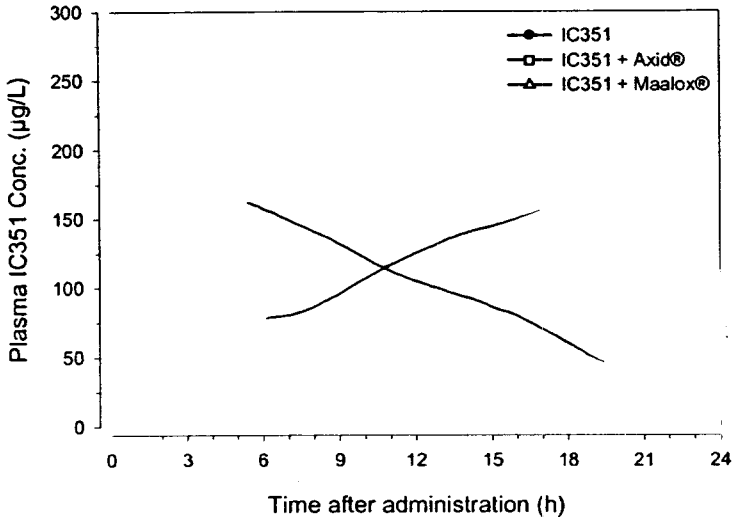
**H6D-EW-LVAR**

**A Study in Healthy Subjects to Investigate the Pharmacokinetics of Tadalafil when Co-administered with Antacid (Maalox ® ) or H2 Antagonist (Axid ® )**

An open-label, three-period, randomised crossover study was conducted in 12 healthy male and female subjects. All subjects received a single oral dose of 10 mg tadalafil on three separate occasions: administered either alone, with an antacid (20 ml Maalox), or with an $H_2$ antagonist (300 mg Nizatidine). Consecutive treatments were separated by a washout period of at least 10 days.




Following table shows geometric mean (CV%) pharmacokinetic parameters of tadalafil (IC351) after oral administration of a single 10 mg Dose of tadalafil alone or with either a 300 mg dose of Axid or a 20 ml dose of Maalox in Healthy Subjects:

| | Treatment | | |
|---|---|---|---|
| Parameter | 10 mg IC351 (N=12) | 10 mg IC351 with 300 mg Axid® (N=12) | 10 mg IC351 with 20 mL Maalox® (N=11) |
| AUC (µg*h/L) | 4096 (30.8) | 4088 (23.3) | 3900 (29.6) |
| AUC(0-$t_n$) (µg*h/L) | 4066 (30.6) | 4050 (23.0) | 3863 (29.6) |
| AUC(0-24) (µg*h/L) | 2557 (22.8) | 2401 (14.3) | 2199 (25.7) |
| $C_{max}$ (µg/L) | 196 (21.9) | 170 (20.9) | 139 (24.9) |
| $t_{max}$ (h)[a] | 2.00 [a] | 2.00 [a] | 4.00 [a] |
| t½ (h) | 16.7 (25.6) | 17.2 (24.4) | 17.7 (27.6) |

- When co-administered with Axid, mean $C_{max}$ was reduced by 14% compared to tadalafil administered alone. The lower 90% CI for the ratio fell just outside the lower limit of — which may suggest an interaction between tadalafil and Axid.
- There was no evidence of an effect on AUC following co-administration of tadalafil with Axid, as the geometric LS means were similar and the 90% CI for the ratio fell within the 0.8 to 1.25 limits.

- There was evidence that 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.
- The 90% CI of geometric mean ratio for $C_{max}$ was outside the 0.80 to 1.25 limits. Median t max occurred approximately 2.5 hours later following dosing of tadalafil with Maalox, compared to tadalafil alone, and the 90% CI for the median difference excluded zero. However, the 90% CI for the geometric mean AUC ratios were within the 0.80 to 1.25 limits.
- Administration of Maalox had no apparent effect on gastric pH but significantly reduced the rate of absorption tadalafil. Conversely, co-administration with Axid markedly increased gastric pH but had little effect on the pharmacokinetics of tadalafil. These results imply that a non-pH-related phenomenon was the cause of the reduced absorption of tadalafil following co-administration with Maalox.

Following table shows the frequency of drug-related treatment-emergent adverse events by type:

| | Number of adverse events [number of subjects with adverse event] | | |
|---|---|---|---|
| COSTART preferred term | 10 mg IC351 (N=12) | 10 mg IC351 & 300 mg Axid® (N=12) | 10 mg IC351 & 20 mL Maalox® (N=11) |
| Back pain | 2[2] | 3[2] | 9[6] |
| Headache | 5[5] | 3[3] | 4[3] |
| Dyspepsia | 3[2] | 0 | 1[1] |
| Vomiting | 0 | 1[1] | 3[1] |
| Myalgia | 0 | 1[1] | 1[1] |
| Arthralgia | 1[1] | 0 | 0 |
| Vasodilatation | 0 | 0 | 1[1] |
| **Total** | **11[8]** | **8[6]** | **19[10]** |

- The most common drug-related adverse events were back pain and headache. There was a greater incidence of back pain when tadalafil was co-administered with Maalox® than when tadalafil was administered alone or with Axid® .