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2.7.2. Summary of Clinical Pharmacology

2.7.2.1. Background and Overview

Previous submissions for tadalafil for the treatment of erectile dysfunction (ED) indication included substantive pharmacokinetic, pharmacodynamic, and clinical pharmacology information following administration of at least 10 mg and generally, 20 mg. The complete content of those submissions is not reproduced in this summary. The clinical pharmacology data package in support of this pulmonary arterial hypertension (PAH) application is largely derived from historical in vitro and clinical pharmacology studies that are represented in previous dossiers and/or in current Cialis® labeling, relevant historical information collected during development of the ED indication is provided for the convenience of the reviewers (Section 2.7.2.1.1). New in vitro and clinical pharmacology studies conducted in support of the PAH indication are described in Section 2.7.2.2.1 and Section 2.7.2.2.2, respectively.

Generally, the pharmacokinetic characteristics of tadalafil over a dose range of 2.5, 5, 10, and 20 mg are very similar, and linear with respect to time and dose. In contrast, and over the entire dose range of 2.5 to 40 mg, a less than proportional increase in systemic exposure is observed, such that following a 40-mg dose compared to that produced by 20 mg, an increase in median maximum plasma concentration (C_{max}) and area under the concentration-time curve at steady state (AUC_{ss}) of 29% and 48%, respectively, is predicted. Furthermore, 81% of the tadalafil AUC_{ss} predicted following 40-mg once-daily administration are within the 5th to 95th percentiles of those estimated following 20 mg. Given the extensive overlap in exposures following 20 mg and 40 mg administration, the magnitude of any pharmacologic effect or drug/drug interaction related to tadalafil plasma concentration would likely be similar with tadalafil doses of 20 mg or 40 mg. Therefore, most aspects of the previous tadalafil clinical pharmacology package are applicable to the present application, including mechanism of action, pharmacodynamics, and intrinsic/extrinsic factors affecting pharmacokinetics. Further, dosing of tadalafil and recommendations for dosage adjustments up to a daily dose of 40 mg, if warranted, may be based upon the simplifying and conservative application of linear, dose-proportional pharmacokinetic behavior as the relative differences or similarities observed from the drug-drug interactions and special population assessments are assumed to remain constant irrespective of the administered dose.

To directly support the PAH indication, 5 additional clinical pharmacology studies using a 40-mg dose (H6D-MC-LVGZ [LVGZ]; H6D-MC-LVHC [LVHC]; H6D-EW-LVHO [LVHO], H6D-EW-LVHL [LVHL]; and H6D-EW-LVHM [LVHM]) were conducted (Table 2.7.2.3). In addition, the disposition of tadalafil and the exploration of an exposure-response relationship using population-based methods has been evaluated from a single Phase 3 study of 389 subjects with PAH receiving placebo or tadalafil (2.5, 10, 20, or 40 mg) once-daily for up to 16 weeks (Study H6D-MC-LVGY [LVGY]). Also, an

in vitro interaction study of tadalafil with P-glycoprotein (P-gp) (ADME Study 2006TP-Pgp02) and an evaluation of mechanism-based inhibition (ADME Study 2003IV-DI001) were conducted (Table 2.7.2.2).

The key pharmacokinetic characteristics of tadalafil pertaining to administration of 40 mg are as follows:

Absorption

Oral absorption of 40-mg tadalafil produces peak plasma concentrations occurring approximately 4 hours after dosing, irrespective of single- or multiple-dose administration with concentrations of total methylcatechol metabolite increasing up to 24 hours postdose after single-dose administration (Study LVGZ).

Modest differences in bioavailability, and thereby apparent volume of distribution (Vz/F) and apparent plasma clearance (CL/F), between doses of 2.5 mg to 20 mg and that following 40 mg administration are likely a reflection of the variation in oral absorption resulting from the low solubility of the drug substance at doses approximating 40 mg (Section 2.7.2.3.1.1).

Food does not affect the rate or extent of tadalafil absorption with tadalafil dosing up to and including 40 mg. Therefore, tadalafil may be administered without regard to meals (Study LVHO).

Distribution

Following oral administration of multiple, once-daily 40-mg doses of tadalafil, the geometric mean (range) Vz/F, is 77.1 (44.3 to 103) L, suggesting that tadalafil is extensively distributed into tissues across doses of 2.5 through 40 mg (Study LVGZ).

Metabolism

It is appropriate to apply the previously established metabolism properties reflected in current Cialis® labeling, to the 40 mg dose.

Elimination

The geometric mean (range) terminal half-life for tadalafil is 15.8 (11.3 to 26.9) hours following multiple-dose daily 40 mg administration (Study LVGZ).

The geometric mean (range) CL/F of tadalafil is 3.39 (2.32 to 5.17) L/hour with modest variability (23.9%) following multiple-dose daily 40 mg administration (Study LVGZ).

Steady-State

The estimate of accumulation, based upon the increase from single to multiple-dose tadalafil AUC and C_{max} approximates 1.3 and is consistent with the half-life of this entity across doses of 2.5 through 40 mg (Study LVGZ).

Tadalafil and total methylcatechol metabolite systemic exposure (AUC and C_{max}) was similar across Days 5 and 10, suggesting that steady-state is likely achieved by Day 5 over the 2.5- to 40-mg dose range (Study LVGZ).

Linearity/Dose Proportionality

Pharmacokinetics of tadalafil and total methylcatechol metabolite following multiple-dose administration were consistent with those observed after single-dose administration, indicating an absence of time-dependent pharmacokinetics (Section 2.7.2.3.1.1).

Comparing the steady-state 40-mg to the 20-mg exposure data provides a geometric mean ratio (90% confidence interval [CI]) of 1.48 (1.30, 1.68). Thus, due to the lack of dose proportionality between 20 mg and 40 mg, a nominal dose of 40 mg provides exposures approximating a 30-mg (90% CI: 26, 34 mg) dose with approximately 81% overlap between exposures (Study LVGY Population PK/PD Report) following 20 mg and 40 mg administration.

Drug Interactions – Pharmacokinetic

In vitro evaluations

In vitro examination of mechanism-based inhibition of cytochrome P450 (CYP)3A4 indicated that diltiazem was a more potent in vitro mechanism-based inhibitor than erythromycin, which was more potent than tadalafil (Study 2003IV-DI001).

Based upon the highest observed tadalafil plasma concentration, the projected in vivo inhibition of metabolism mediated by CYPs 3A, 2C9, 1A2, and 2C19 would be 7.3%, 4.7%, 19.1%, and 4.3% respectively. Thus, in vitro studies predict that 40-mg tadalafil would not cause clinically significant inhibition of the metabolic clearance of drugs metabolized via these isoforms (Study LVHM).

Tadalafil was found in vitro to be a P-gp substrate; however, the data indicate that the pharmacokinetics of tadalafil would be unaffected by coadministration of a P-gp inhibitor in vivo due to the rapid passive permeability into blood. Assessments also suggested the potential for inhibition of P-gp by tadalafil (Study 2006TP-Pgp02).

In vivo evaluations

Should a new drug or existing entity have attributes of drug metabolism such that the drug is characterized as a substrate of a specific enzyme, then in vivo studies that evaluate inhibitors and/or inducers of that enzyme are appropriate. Also, when a new drug or existing entity shows the potential for inhibition or induction of an enzyme, then

an in vivo study of that specific effect on a specific substrate is an appropriate evaluation. Both of these types of in vivo assessments of drug interaction potential have been performed for tadalafil. Collectively, based upon the historical data and that provided in support of the PAH indication, these results demonstrate the potential effects of other drugs on tadalafil as well as the potential effects of tadalafil on other drugs. The following are the in vivo drug interaction studies that have been evaluated for the PAH indication.

Interaction with Bosentan

Bosentan 125 mg twice-daily did not alter tadalafil (40 mg once-daily) exposure after single-dose administration; however, following 10 days of coadministration mean tadalafil CL_{ss}/F and V_z/F_{ss} were increased by approximately 70% and 53% with associated decreases in tadalafil AUC_τ (41.5%) and C_{max} (26.6%) (Study LVGZ). A strong relationship between tadalafil clearance and concomitant bosentan use was also observed in the population analysis of PAH subjects, with tadalafil clearance increasing from 1.59 to 2.79 L/h in those subjects receiving bosentan, representing a decrease of approximately 35% in the median AUC_{ss} with bosentan (Study LVGY Population PK/PD Report). These results indicate that potent CYP3A inducers (rifampin) lower systemic exposure of tadalafil to a greater extent than moderate CYP3A4 inducers (Study LVGZ).

Coadministration of tadalafil and bosentan did not discernibly alter exposure to bosentan or its metabolites following single- and multiple-dose administration (Study LVGZ).

Interaction with Digoxin

Although in vitro studies suggest that tadalafil is a potential inhibitor of P-gp transporter, once-daily oral administration of tadalafil 40 mg does not alter the AUC, C_{max}, or C_{min} of steady-state digoxin, a substrate of P-gp (Study LVHL).

Interaction with Oral Contraceptives

Administration of oral contraceptive with single 40-mg doses of tadalafil resulted in higher AUC (54%) and C_{max} (90%) of ethinylestradiol; following multiple-doses of oral contraceptive with tadalafil (40 mg once-daily) for 21 days increases in both AUC (26%) and C_{max} (70%) of ethinylestradiol were observed relative to oral contraceptive and placebo. There was no statistically significant effect of tadalafil on levonorgestrel pharmacokinetics following single- and multiple-dose oral contraceptive administration (Study LVHM).

Pharmacokinetics in Subjects with PAH

Plasma tadalafil pharmacokinetics in subjects with PAH are in agreement to those in subjects with ED receiving equivalent doses and regimens. For both ED and PAH, tadalafil disposition is described by a one-compartment model with no patient-specific factor identified warranting clinical consideration of a dosage adjustment based upon

pharmacokinetics alone. Therefore, properties observed in ED subjects are applicable to those with PAH (Section 2.7.2.3.1.2).

In subjects with PAH not receiving concomitant bosentan, the median steady-state exposure is 26% higher than that in healthy volunteers following 40 mg administration. Generally, tadalafil systemic exposures in subjects with PAH are comparable to those in healthy subjects; therefore, properties observed in healthy subjects are applicable to subjects with PAH (Section 2.7.2.3.1.2).

Pharmacokinetics in Special Populations

It is appropriate to apply the previous pharmacokinetic data reported in special populations and reflected in current Cialis®labeling to the 40 mg dose, with the addition of those provided as follows.

Gender - Several assessments of the tadalafil pharmacokinetics have demonstrated that the exposure is similar between males and females (Section 2.7.2.3.2.1).

Ethnicity - Pharmacokinetic studies have included subjects and patients from different ethnic groups, and no meaningful differences in the typical exposure to tadalafil have been identified (Section 2.7.2.3.2.2).

Exposure-Response in Subjects with PAH

An analysis of tadalafil exposure and 6-minute walk distance in subjects with PAH, assuming a baseline value of 321 meters, predicted a median (10th to 90th percentile) response of 39.6 meters (36.3 to 45.3 meters) and 35.9 meters (32.2 to 41.0 meters) without and with bosentan, respectively, at steady-state exposures following 16 weeks of 40 mg daily administration (Section 2.7.2.2.2.5).

2.7.2.1.1. Summary Results across Studies Conducted in Support of the ED Indication

2.7.2.1.1.1. Historical In Vitro Studies

Using human biomaterials, the percentage binding to human plasma proteins, distribution into whole blood, the pathway of metabolism, and the in vitro interaction potential on CYP were investigated and included in previous applications (see Table 2.7.2.5.1 and Table 2.7.2.5.2 in Appendix 2.7.2.5). Section 2.7.2.1.1.2 presents these data in the context of the appropriate clinical pharmacology information.

2.7.2.1.1.2. Historical Clinical Pharmacology Studies

The pharmacokinetics and pharmacodynamics of tadalafil have been extensively evaluated in single- and multiple-dose clinical pharmacology studies and population-based pharmacokinetic analysis of data from 4 clinical trials in support of the ED indication. Safety data from studies conducted in support of the ED indication in addition to the new studies in support of the PAH indication are reported in the Summary

of Clinical Safety (Section 2.7.4.5.9). The pharmacokinetic results from the studies are organized into listings in the appendix to this summary (Table 2.7.2.5.3).

2.7.2.1.1.2.1. Healthy Subject PK, PD, Safety, and Tolerability

Tadalafil in plasma is 94% bound to proteins, principally albumin and α_1-acid glycoprotein (ADME 25 and 26). Protein binding is unaffected by renal impairment and is independent of tadalafil and metabolite concentration (Study H6D-EW-LVAJ [LVAJ]).

Tadalafil is cleared extensively by oxidative metabolism to produce the catechol metabolite (IC711), and CYP3A4 is the predominant enzyme in the oxidative metabolism of tadalafil (ADME 34). This oxidative metabolite is further metabolized to form the methylcatechol and the methylcatechol glucuronide conjugate with the methylcatechol glucuronide as the major metabolite in human plasma and urine (Study H6D-LC-LVAA [LVAA]). Pharmacokinetic assessment has shown that the methylcatechol is present at levels generally less than 10% of the total (LVAJ, H6D-EW-LVAU [LVAU], and H6D-EW-LVDK [LVDK]). [redacted] This metabolite is not selective for phosphodiesterase 5 (PDE5) and is at least 13,000-fold less potent for PDE5 than tadalafil (Nonclinical Pharmacology Report 09).

Approximately 61% of a 100 mg (100 µCi) dose of tadalafil was excreted in feces and approximately 36% was recovered in urine (Study LVAA). There is negligible renal clearance of the parent drug as shown by the low recovery of intact tadalafil in urine (Studies H6D-MC-LVBS [LVBS] and LVAA). The kidney, however, is a route of excretion that is more predominant for the glucuronide metabolites (Studies LVAA, LVAJ, and H6D-EW-LVDT [LVDT]). Biliary secretion is presumed to be an important route of elimination of tadalafil and its metabolites (Study LVAA).

Table 2.7.2.1 provides the dose normalized pharmacokinetics pooled across 13 clinical pharmacology studies and submitted in previous dossiers supporting the ED indication. In healthy subjects, CL/F of tadalafil is 2.48 L/h, indicating a low hepatic extraction ratio. The mean half life ($t_{1/2}$) for tadalafil is 17.5 hours and essentially similar to that for total methylcatechol, indicating that elimination of the metabolites is formation-rate limited (Study LVDK). During tadalafil 20 mg once-daily dosing, steady-state plasma concentrations are attained within approximately 5 days and the degree of accumulation is approximately 1.6-fold (Study LVDK).

Table 2.7.2.1. Dose-Normalized (20 mg) Tadalafil Pharmacokinetics following Tadalafil 10 mg or 20 mg Single Dose to 237 Healthy Subjects

Parameter (unit)	5th Percentile	Geometric Mean (CV%)	95th Percentile
AUC (µg*h/L)	4597	8066 (39.3)	14844
C_{max} (µg/L)	239	378 (27.6)	576
t_{max} (h)	-	2.0 (0.5 to 12.0) [a]	-
$t_{1/2}$ (h)	11.5	17.5 (32.3)	29.6
CL/F (L/h)	1.35	2.48 (39.3)	4.35
V_z/F (L)	39.5	62.6 (25.4)	92.1

Abbreviations: AUC = area under the plasma concentration versus time curve; CL/F = apparent oral clearance; C_{max} = maximum observed plasma concentration; CV = coefficient of variation, $t_{1/2}$ = terminal elimination half-life; t_{max} = time of C_{max}; Vz /F = apparent volume of distribution.

[a] Median and range.

Note: The 13 studies include Studies H6D-EW-LVAH, H6D-EW-LVAI, H6D-EW-LVAJ, H6D-EW-LVAK, H6D-EW-LVAL, H6D-EW-LVAR, H6D-EW-LVAU, H6D-EW-LVAZ, H6D-EW-LVBX, H6D-EW-LVBW, H6D-EW-LVCA, H6D-EW-LVDL, and H6D-EW-LVDQ.

Tadalafil is rapidly absorbed after oral administration, with C_{max} in plasma occurring at a median t_{max} of 2 hours with doses up to 20 mg. Tadalafil pharmacokinetics are linear with respect to time and dose over a range of 2.5 to 20 mg (H6D-EW-LVBX [LVBX] and LVDK). The intrasubject variability estimated from the pooled analyses across 13 clinical pharmacology studies for the AUC and C_{max} were 13.3% and 15.8%, respectively.

2.7.2.1.1.2.2. Effect of Intrinsic Factors

There is an approximately (20%) reduction in mean oral clearance with age (Studies H6D-MC-LVBU [LVBU], H6D-MC-LVBH [LVBH], H6D-EW-LVBW [LVBW]). In female subjects, steady-state tadalafil concentrations were slightly (13%) higher than in male subjects (Study H6D-EW-LVAD [LVAD]).

Tadalafil pharmacokinetics in healthy male Japanese and Caucasian subjects were comparable at doses of 5, 10, and 20 mg, with a slightly lower exposure in Japanese subjects at 40 mg (Study H6D-EW-LVCS [LVCS]). Similarly, tadalafil pharmacokinetics following doses of 10 and 20 mg in Chinese subjects (Study H6D-EW-LVFU [LVFU]) were generally similar to those in Japanese and Caucasian subjects. Furthermore, population-based analyses of tadalafil pharmacokinetics in Caucasian and Japanese ED patients revealed that exposures were similar across both groups and no dosage adjustment was warranted.

In subjects with diabetes, systemic exposure to tadalafil was 19% lower than in matched healthy subjects (Study H6D-EW-LVAS [LVAS]).

In 2 clinical pharmacology studies of 5- to 20-mg single tadalafil doses in subjects with mild renal insufficiency (creatinine clearance 51 to 80 mL/min), moderate insufficiency

(creatinine clearance 31 to 50 mL/min) (Study LVAJ), or end-stage renal disease on dialysis (Study LVDT), exposure in subjects with renal insufficiency was approximately double that in healthy subjects. Across subjects with renal insufficiency, systemic exposure to total methylcatechol metabolite was approximately 3-fold higher than in healthy subjects, and the mean $t_{1/2}$ was prolonged (approximately 50 hours) (Studies LVAJ and LVDT). Hemodialysis contributed negligibly to tadalafil elimination (Study LVDT).

Systemic exposure to tadalafil in subjects with hepatic cirrhosis characterized as either very mild (fatty liver on sonography), mild (Child-Pugh Class A), or moderate cirrhosis (Child-Pugh Class B) was similar to that in age-matched healthy subjects (Study H6D-EW-LVAK [LVAK]).

2.7.2.1.1.2.3. Effect of Other Drugs on the Pharmacokinetics of Tadalafil

Coadministration of an histamine (H_2)-antagonist (nizatidine) has negligible effects on tadalafil pharmacokinetics (H6D-EW-LVAR [LVAR]). Coadministration of a magnesium/aluminum hydroxide antacid (Maalox®) reduces the rate but not the extent of tadalafil absorption (Study LVAR).

In healthy subjects, concurrent dosing with a selective CYP3A4 inducer (rifampicin, 600 mg daily) increased tadalafil oral clearance, thereby reducing tadalafil AUC by 88% and C_{max} by 46% relative to the values for administration of tadalafil as a single agent (Study H6D-EW-LVAZ [LVAZ]). A selective and potent CYP3A4 inhibitor (ketoconazole, 400 mg daily) increased tadalafil 20 mg AUC by 312% and C_{max} by 22% (Study H6D-EW-LVEV [LVEV]). Ketoconazole (200 mg daily) increased tadalafil 10 mg AUC by 107% and C_{max} by 15% (Study LVAZ). These data confirm that CYP3A4 is the predominant enzyme involved in clearance of tadalafil.

Ritonavir, an inhibitor of the CYPs 3A4, 2C9, 2C19, and 2D6 at a dose of 200 mg twice daily, increased 20-mg tadalafil AUC by 124% with no change in C_{max} (Study LVEV). In a subsequent study, 500-mg ritonavir and 600-mg ritonavir twice a day (Study H6D-EW-LVFV [LVFV]) increased the AUC of 20-mg tadalafil by 32%, with a decrease in C_{max} of 30%. These results are consistent with ritonavir's activity as a dose- and time-dependent inducer of the CYP3A4 pathway, as well as its activity as an inhibitor, with induction being greater after prolonged dosing regimens and at higher ritonavir dose levels.

2.7.2.1.1.2.4. Effect of Tadalafil on the Pharmacokinetics of Other Drugs

Studies with human liver microsomes indicate that tadalafil has negligible potential for clinically significant competitive inhibition of CYP (ADME 4 and 89). Clinical pharmacology studies of tadalafil with coadministration of probe 3A4 substrates

(midazolam [Study H6D-EW-LVAF (LVAF)] and lovastatin [Study H6D-EW-LVDM (LVDM)]) provided strong evidence that tadalafil does not cause clinically significant differences in clearance of drugs metabolized by CYP3A4. There was no effect of tadalafil on the pharmacokinetics or pharmacodynamics of the probe substrates theophylline (Study H6D-EW-LVAP [LVAP]), warfarin (Studies H6D-EW-LVAQ [LVAQ] and H6D-EW-LVEX [LVEX]), metoprolol (H6D-EW-LVAW [LVAW]) and alcohol (Studies H6D-EW-LVAE [LVAE] and H6D-EW-LVET [LVET]), indicating that tadalafil will not alter the metabolism of drugs by CYPs 1A2, 2C9, 2C19, 2D6, 2E1.

2.7.2.1.1.2.5. Pharmacodynamic Drug Interaction Studies

2.7.2.1.1.2.5.1. Pharmacodynamic Interaction Studies between Tadalafil and Alcohol

When ethanol is consumed in an amount up to 0.6 g/kg, no pharmacodynamic interaction is expected with coadministration of tadalafil 10 or 20 mg. In addition, no pharmacodynamic interaction was observed with coadministration of ethanol 0.7 g/kg and tadalafil 10 mg. However, caution should be exercised with tadalafil 20 mg use when ethanol is consumed in an amount that would achieve intoxication.

2.7.2.1.1.2.5.2. Pharmacodynamic Interaction Studies between Tadalafil and Nitrates

Study H6D-LC-LVBY (LVBY) demonstrated that tadalafil 5 mg administered once-daily would likely augment the hypotensive effect of nitrates. Study H6D-EW-LVDN (LVDN) demonstrated that the nitrate interaction following tadalafil 20 mg dosed to steady-state resolved by 48 hours following the last tadalafil dose. For a subject taking 40 mg daily for PAH where nitrate administration is deemed medically necessary in a life-threatening situation, at least 48 hours should elapse after the last dose of tadalafil before nitrate administration is considered. In such circumstances, nitrates should only be administered under close medical supervision with appropriate hemodynamic monitoring.

2.7.2.1.1.2.5.3. Pharmacodynamic Interaction Studies between Tadalafil and Alpha Blockers

Six studies were conducted with α-adrenergic receptor-blocking agents and have been reported in previous submissions in the US and Europe.

In subjects receiving concomitant tadalafil (20 mg single-dose) and doxazosin (8 mg daily), an alpha (1)adrenergic receptor blocker, there was an augmentation of the blood-pressure-lowering effect of doxazosin. This effect was still present at 12 hours postdose and had generally disappeared at 24 hours. The number of subjects with potentially clinically significant standing-blood-pressure decreases was greater for the combination (Study H6D-EW- LVFG [LVFG]). An additional study was performed with

tadalafil (20 mg single-dose) and doxazosin (4 and 8 mg daily) using Ambulatory Blood Pressure Monitoring, and this showed that the augmentation appeared unrelated to dosing times and resulted in a greater number of outliers for the combination than had been observed in the previous study (Study H6D-EW-LVFT [LVFT]). Both of these studies had some symptomatology associated with these blood pressure changes. A further study was carried out with doxazosin (up to 4 mg daily) added to tadalafil (5 mg daily) and again there was an augmentation of response (Study H6D-EW-LVGT[LVGT]). In this clinical pharmacology study, there were symptoms associated with the decrease in blood pressure, including syncope. An interaction study with tadalafil (20 mg single dose) and alfuzosin, also an alpha (1) adrenergic receptor blocker, showed no clinically significant effect on blood pressure (SANOFI-SYNTHELABO 2004). In two clinical pharmacology studies in healthy volunteers, tadalafil (5 mg daily, and 10 mg and 20 mg single-dose) had no clinically significant effect on blood pressure changes due to tamsulosin, a selective alpha (1A)-adrenergic receptor blocking agent (Studies H6D-EW-LVAY [LVAY] and H6D-EW-LVGN [LVGN]). It is not known how this extrapolates to other alpha (1A)-adrenergic receptor blocking agents.

2.7.2.1.1.2.5.4. Pharmacodynamic Interaction Studies between Tadalafil and Antihypertensives

Data obtained from clinical pharmacology studies evaluating the effect of tadalafil on the pharmacodynamic effect of antihypertensives in patients with hypertension (Table 2.7.2.5.5) indicated that no apparent dose effect of tadalafil on blood pressure. When administered to healthy subjects, 20-mg tadalafil produced no significant difference compared to placebo in supine systolic and diastolic blood pressure (difference in the mean maximal decrease of 1.6/0.8 mm Hg, respectively) and in standing systolic and diastolic blood pressure (difference in the mean maximal decrease of 0.2/4.6 mm Hg, respectively), and the mean values for maximum decrease in systolic blood pressure were similar on dosing Days 1 and 10 (Study LVDK). In addition, there was no significant effect on heart rate.

Studies in healthy subjects with a calcium antagonist were also performed (Studies H6D-EW-LVAV [LVAV] and H6D-EW-LVDP [LVDP]). In hypertensive subjects, interaction studies were performed with a beta blocker (Study LVAW), a thiazide diuretic (Study H6D-EW-LVAX [LVAX]), and an angiotensin-converting enzyme (ACE) inhibitor (Study H6D-EW-LVBC [LVBC]). There was no evidence of a clinically significant pharmacodynamic interaction in any of these studies.

In 2 further studies performed in subjects taking multiple antihypertensive therapy (Studies H6D-EW-LVDS [LVDS] and H6D-EW-LVDV [LVDV]), changes in ambulatory blood pressure appeared to be related to the degree of blood pressure control.

In a separate clinical pharmacology study of the interaction between theophylline (a non-specific inhibitor of PDE) and tadalafil (a selective PDE5), a small but clinically

unimportant increase in heart rate was detected with no concurrent changes in blood pressure (Study LVAP).

2.7.2.1.1.2.5.5. Pharmacodynamic Interaction Studies between Tadalafil and Anticoagulants

2.7.2.1.1.2.5.5.1. Pharmacodynamic Interaction Studies with Aspirin

Chronic dosing with aspirin is commonly used to prevent thrombosis. It is anticipated that a proportion of patients receiving tadalafil will also receive aspirin at some time. Platelet activation is regulated by a number of factors, including changes in the levels of cyclic nucleotides, calcium influx, and protein phosphorylation. There is potential for agents that increase cGMP levels to interfere with the pathways of platelet aggregation.

In studies in healthy males (H6D-EW-LVBV [LVBV], H6D-EW-LVEY [LVEY]), once-daily administration of 300-mg aspirin prolonged mean bleeding time when compared with pre-aspirin bleeding time. There was no clinically significant increase in mean bleeding times following coadministration of aspirin with placebo or tadalafil 10 or 20 mg. Thus, coadministration of tadalafil did not affect the aspirin-induced bleeding time increases.

2.7.2.1.1.2.5.5.2. Pharmacodynamic Interaction Studies with Warfarin

Warfarin is used mainly to reduce the risk of embolism in coronary or venous thrombosis. Many factors, including the administration of other drugs, can interfere with its actions. This can be dangerous if anticoagulation occurs beyond a safe level, leading to abnormal bleeding and hemorrhaging. Conversely, any interaction inhibiting the anticoagulant effect could worsen the underlying disease for which warfarin was prescribed.

When warfarin was coadministered with 10- or 20-mg tadalafil in healthy males (H6D-EW-LVAQ [LVAQ], H6D-EW-LVEX [LVEX]), there was no clinically significant change in the pharmacodynamic effect of warfarin to increase prothrombin time.

Since coadministration of 10- and 20-mg tadalafil did not induce a clinically significant effect on the anti-coagulation action of aspirin and warfarin, coadministration of these drugs and tadalafil is believed to be safe (Section 2.7.4).

2.7.2.1.1.2.6. Thorough QT Interval Study

A thorough QT study was performed to demonstrate the effect of a single 100-mg dose of tadalafil on cardiac electrophysiology in Study H6D-EW-LVFB (LVFB). This dose , was chosen because it yields exposures expected following coadministration of tadalafil 20 mg with potent CYP3A4 inhibitors or those observed in renal impairment. Relative to

the ICH E14 Guidance, Section 2.2.4, Study LVFB was negative, as the upper bound of the 95% one-sided confidence interval for the largest time-matched mean effect of the drug on the QTc was 5.1 ms (thereby excluding the 10 ms threshold).

2.7.2.1.1.2.7. Special Studies

2.7.2.1.1.2.7.1. Effects on Visual Function and Color Vision

Single 10-, 20-, and 40-mg doses of tadalafil had no effect on color vision or visual function in healthy subjects (Studies H6D-EW-LVAN [LVAN], H6D-EW-LVCN [LVCN], and H6D-EW-LVFF [LVFF]).

2.7.2.1.1.2.7.2. Effect on Renal Blood Flow

Single 20- and 80-mg doses of tadalafil had no effect on effective renal plasma flow as assessed by renal radionuclide scan in healthy, young male subjects (Study H6D-EW-LVFA [LVFA]). In addition, there was no effect on lumbar and gluteal venocongestion assessed by FDG-positron emission tomography (PET) and magnetic resonance imaging (MRI) scans. This study also showed that single 20- and 80-mg doses of tadalafil had no effect compared to placebo on the presence of inflammatory or myolytic biomarkers.

2.7.2.1.1.2.7.3. Effect on Myocardial Blood Flow

Three studies were conducted in subjects with coronary artery disease (Studies LVBY, H6D-MC-LVCP [LVCP], and Study H6D-LC-LVBZ [LVBZ]). In subjects with coronary artery disease undergoing exercise stress testing, 10-mg tadalafil did not significantly reduce the total exercise time or time to ischemia compared to placebo (Study LVCP). In Study LVBZ, 20-mg tadalafil had no significant effect on myocardial blood flow, as assessed by PET, both at rest and during pharmacological stress.

2.7.2.1.1.2.8. Population Pharmacokinetics and/or Population PK/PD

Population pharmacokinetic models were previously developed in three Phase 3 studies, H6D-MC-LVCE (LVCE, N=229), H6D-MC-LVDI (LVDI, N=253) and H6D-MC-LVDJ (LVDJ, N=188). The population analyses characterized tadalafil pharmacokinetics in male subjects with ED following as-needed administration of tadalafil for 12 weeks. Age, weight, cardiovascular, diabetes, indices of hepatic and renal function, smoking status, alcohol consumption, ethnicity (LVDI/LVDJ), ED, and duration were investigated as potential covariates of CL/F and V/F. A one-compartment model parameterized in terms of first order rate absorption (ka), CL/F, and V/F provided the most appropriate description of tadalafil concentrations in these studies. Consistently, across all 3 studies, no subject-specific factors warranting clinical consideration of dosing regimen adjustments were identified.

Similarly, the population pharmacokinetics of tadalafil were determined in male subjects with ED following once-a-day administration of 2.5- and 5-mg tadalafil in the Phase 3 Study H6D-MC-LVFP (LVFP). The pharmacokinetics of tadalafil were again described by a one-compartment model and no patient-specific factor warranting dosing adjustments was identified. Moreover, the absorption, distribution, metabolism, and excretion of tadalafil were similar irrespective of as-needed or once-a-day administration indicating that systemic exposure to tadalafil was comparable between these regimens at equivalent doses and dosing intervals.

2.7.2.2. Summary Results of Individual Studies

2.7.2.2.1. In Vitro Studies

As tadalafil is metabolized by CYP3A4 and includes a methylenedioxy functional group in its chemical structure, the possibility of mechanism-based inhibition of CYP3A had been evaluated previously and has been further investigated and summarized below (Table 2.7.2.2). Further, an in vitro interaction study of tadalafil with P-gp was conducted using 2 in vitro models.

Table 2.7.2.2. Index of In Vitro Studies Using Human Biomaterials that Support Clinical Development

Study ID	Study Title
2003IV-DI001	Kinetic Examination of Mechanism-Based Inhibition of Cytochrome P450 3A4 by Tadalafil
2006TP-Pgp 02	Use of In Vitro Models to Assess the Interaction of LY450190 with P-glycoprotein

2.7.2.2.1.1. In Vitro Interaction with Human CYP3A4

Study 2003IV-DI001: Kinetic Examination of Mechanism-Based Inhibition of Cytochrome P450 3A4 by Tadalafil

Tadalafil had been shown in a previous in vitro study in human microsomes to be a weak mechanism-based inhibitor of CYP3A in a time- and concentration-dependent manner (ADME 5). In order to assess the relative potency to other known mechanism based inhibitors this additional kinetic examination was conducted in vitro in human microsomes. Results from this kinetic examination with 2 positive controls indicated that diltiazem was a more potent in vitro mechanism-based inhibitor than erythromycin, which was more potent than tadalafil.

2.7.2.2.1.2 In Vitro Interaction with P-glycoprotein

Study 2006TP-Pgp02: **Use of In Vitro Models to Assess the Interaction of LY450190 with P-glycoprotein**

Tadalafil was found in vitro to be a P-gp substrate; however, the data indicate that the pharmacokinetics of tadalafil would be unaffected by coadministration of a P-gp inhibitor in vivo due to the rapid passive permeability into blood. In membrane vesicles, inhibition of the P-gp substrate vinblastine by tadalafil suggested inhibition of P-gp mediated transport was possible in vivo. A clinical study (Study LVHL, Section 2.7.2.2.2.4) demonstrated that there was no statistically significant effect of multiple 40-mg doses of tadalafil on the steady-state pharmacokinetics or renal clearance of digoxin, indicating that tadalafil does not alter P-gp activity in vivo.

2.7.2.2.2. Clinical Pharmacology Studies

In support of the PAH application, the pharmacokinetics and pharmacodynamics of tadalafil were examined in 3 multiple-dose clinical pharmacology studies and a population analysis from a Phase 3 study (Table 2.7.2.3). Further, the drug interaction potential of tadalafil on bosentan, oral contraceptives and digoxin were determined (Table 2.7.2.3). Module 5 contains the clinical study reports (CSRs) for these studies.

Table 2.7.2.3. Index of Pharmacokinetic and Pharmacodynamic Studies and Analyses

Brief Description of Study	Trial Alias
Healthy Subject PK, PD, and Tolerability	
Single & multiple-dose, PK, safety, tolerability (40 mg)	**LVGZ**
Multiple dose, PK, safety, Japanese (40 mg)	**LVHC**
Effect of Intrinsic Factors	
Single & multiple-dose PK, safety, tolerability, females (40 mg)	**LVHM**
Effect of Other Drugs on Tadalafil PK	
Effect of bosentan	**LVGZ**
Effect of oral contraceptives	**LVHM**
Effect of Tadalafil on PK of Other Drugs	
Effect of tadalafil (40 mg) on bosentan	**LVGZ**
Effect of tadalafil on digoxin	**LVHL**
Phase 3 Studies Providing Population PK and/or PD Information	
PDE5 inhibitor (tadalafil) in the treatment of patients with PAH (2.5, 10, 20, 40 mg)	**LVGY**

Abbreviations: PAH = pulmonary arterial hypertension; PD = pharmacodynamics; PDE5 = phosphodiesterase 5; PK = pharmacokinetics.

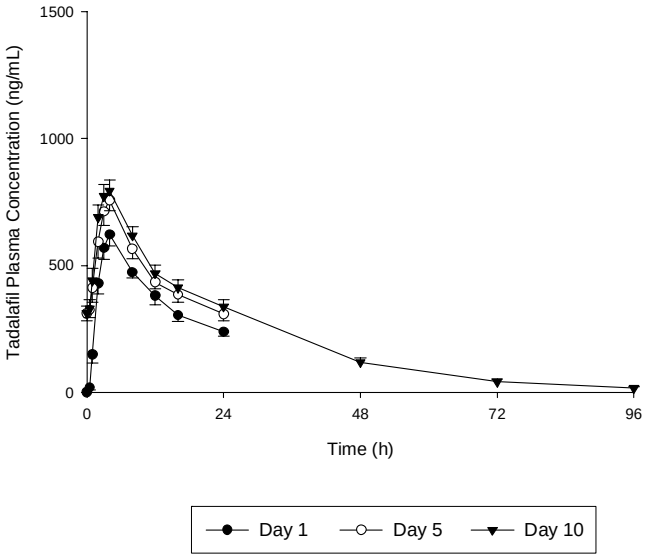
2.7.2.2.2.1. Healthy Subject PK, PD, Safety, and Tolerability

The following studies were conducted in healthy subjects to assess the pharmacokinetics, pharmacodynamics, safety, and tolerability of tadalafil in support of the PAH indication.

LVGZ **A Pharmacokinetic Interaction Study Between Tadalafil and Bosentan in Healthy Male Subjects**

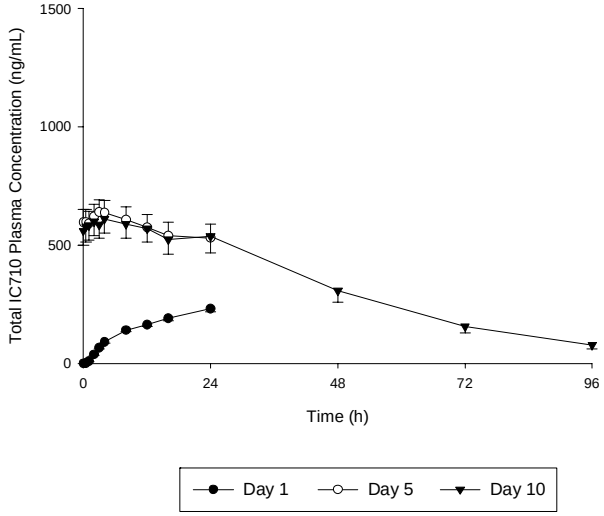
This was a randomized, open-label, 3-period, crossover study conducted in 15 healthy adult male subjects (19 to 52 years) to assess the pharmacokinetics, safety, and tolerability of tadalafil and bosentan when administered alone and together. Subjects received a total of 3 treatments: 40-mg tadalafil once-daily for 10 days, 125-mg bosentan twice daily for 10 days, and the combination of tadalafil and bosentan for 10 days, with each period being separated by at least a 7-day washout. All doses were administered at least 30 minutes after a meal, and each dose of bosentan was administered approximately 12 hours after the previous dose. Only the data for 40-mg tadalafil once-daily administration are presented in this section. Section 2.7.2.2.2.3 and Section 2.7.2.2.2.4 summarize the results reflecting the interaction potential between tadalafil and bosentan.

Results and Conclusions: Figure 2.7.2.1 and Figure 2.7.2.2 illustrate mean concentrations of tadalafil and methylcatechol glucuronide (total IC710), respectively, following once-daily administration of 40-mg tadalafil on Study Days 1, 5, and 10. Maximum plasma concentrations of tadalafil were achieved about 4 hours after dosing, irrespective of single- or multiple-dose administration, and appeared to decline in a monoexponential fashion. Plasma concentrations of total methylcatechol metabolite continuously increased up to 24 hours postdose on Study Day 1. On Study Days 5 and 10, plasma concentrations of total methylcatechol metabolite were maintained throughout the dosing interval of 24 hours without appreciable elimination. On Study Day 10, and after 24 hours, total methylcatechol metabolite concentrations demonstrated a monoexponential decay.



Source: CSR LVGZ, Figure LVGZ.7.1

Figure 2.7.2.1. **Tadalafil arithmetic mean (±SEM) plasma concentration time profiles on Study Day 1, 5, and 10 following multiple doses of 40-mg tadalafil once-daily for 10 days.**



Source: CSR LVGZ, Figure LVGZ.7.2

Figure 2.7.2.2. **Total methylcatechol (total IC710) metabolite arithmetic mean (±SEM) plasma concentration time profiles on Study Day 1, 5, and 10 following multiple doses of 40-mg tadalafil for 10 days.**

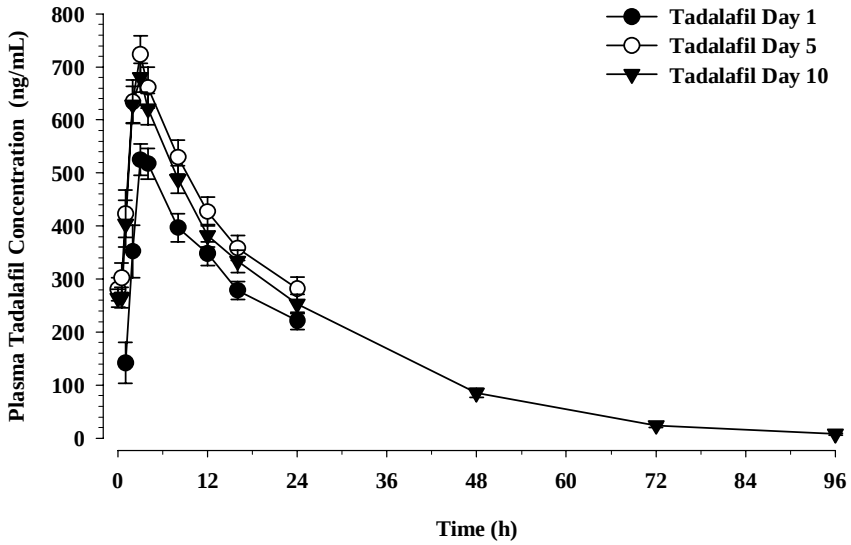
Tadalafil systemic exposure (AUC and C_{max}) was similar across Study Days 5 and 10, suggesting that steady-state was likely achieved by Study Day 5; furthermore, CL_{ss}/F appeared stationary between Study Days 5 and 10, indicating an absence of time-dependent tadalafil pharmacokinetics and consistent with the data reported following

multiple doses of 10 and 20 mg. The estimate of tadalafil accumulation is approximately 1.3-fold for both AUC and C_{max} and that for total methylcatechol metabolite is 3- to 4-fold.

LVHC **A Study to Examine the Safety and Pharmacokinetics of Tadalafil (40 mg or Placebo) in Healthy Adult Japanese Subjects during Multiple Oral Administration**

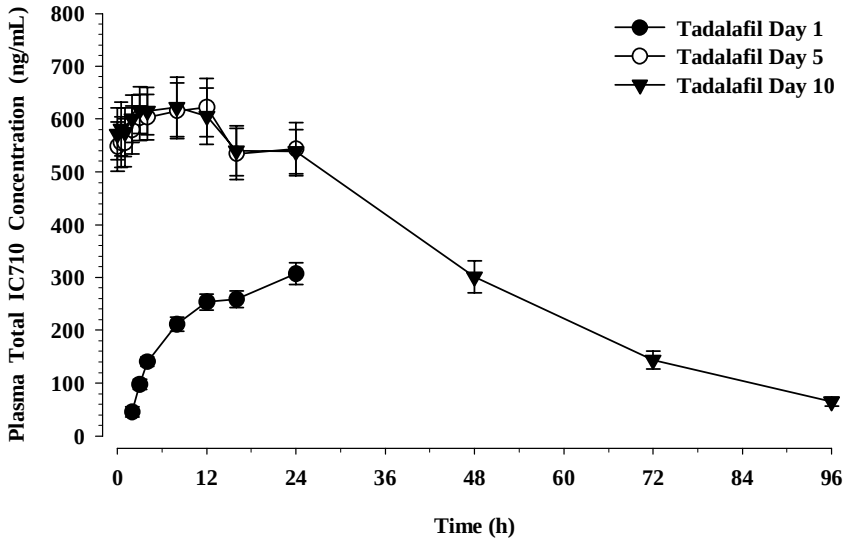
This was an investigator- and subject-blind, randomized, placebo-controlled study conducted in 24 healthy Japanese subjects (13 males and 11 females, 20 to 29 years) to examine the safety of 40-mg tadalafil and to assess the multiple-dose pharmacokinetics of tadalafil and total methylcatechol metabolite (total IC710). Subjects received 40-mg tadalafil or placebo once-daily in the morning for 10 days. All doses were administered at least 30 minutes after a meal.

Results and Conclusions: Figure 2.7.2.3 and Figure 2.7.2.4 illustrate the mean plasma concentration-time profiles for tadalafil and total methylcatechol metabolite (total IC710) following once-daily administration of 40-mg tadalafil on Study Days 1, 5, and 10. Maximum plasma concentrations of tadalafil were achieved at about 3 hours postdose, irrespective of single or multiple-dose administration, and then appeared to decline in a monoexponential fashion. Steady-state is achieved by Study Day 5 for both tadalafil and total methylcatechol metabolite following once-daily administration of 40-mg tadalafil. The estimates of accumulation are approximately 1.3-fold for both tadalafil AUC and C_{max} and approximately 3-fold for total methylcatechol metabolite and stationary over Study Days 5 and 10.



Source: CSR LVHC, Figure LVHC.7.1

Figure 2.7.2.3. **Arithmetic mean (±SEM) tadalafil plasma concentration time profiles on Study Day 1, 5, and 10 following multiple once daily doses of 40-mg tadalafil.**



Source: CSR LVHC, Figure LVHC.7.2

Figure 2.7.2.4. **Arithmetic mean (±SEM) total IC710 plasma concentration time profiles on Study Day 1, 5, and 10 following multiple once daily doses of 40-mg tadalafil.**

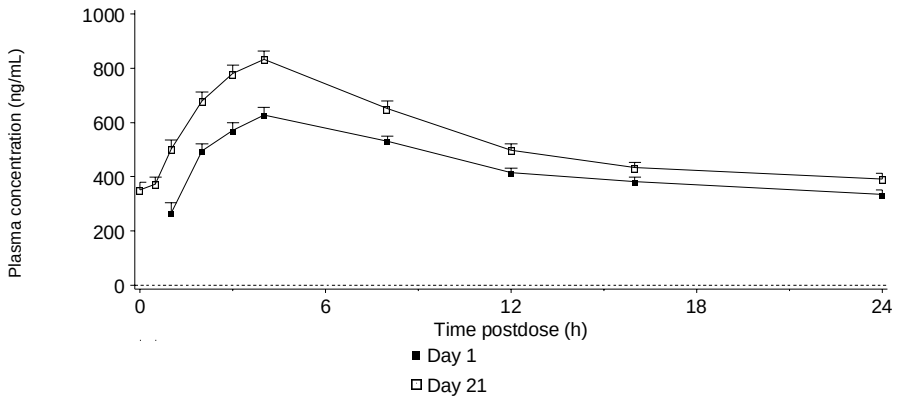
2.7.2.2.2.2. Effect of Intrinsic Factors

In female subjects, mean steady-state tadalafil exposure following 10 mg daily administration were previously determined to be slightly (13%) higher than in male subjects (Study LVAD). This small gender effect was not considered to be clinically important; however, given the 2:1 prevalence of idiopathic PAH in females compared to males, the pharmacokinetics, safety, and tolerability of tadalafil were evaluated in females following 40-mg tadalafil administration in the presence of oral contraceptives.

LVHM **A Pharmacokinetic Interaction Study Between Tadalafil and Oral Contraceptives in Healthy Female Subjects**

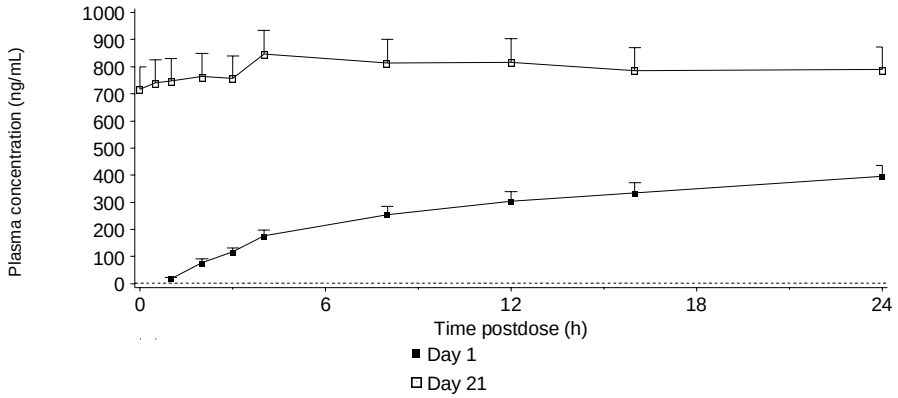
Section 2.7.2.2.2.4 contains a description of the study design for Study LVHM. As it is assumed that if any interaction between oral contraceptives, principally ethinylestradiol, and tadalafil were to occur, tadalafil would be the perpetrator of the effect rather than be influenced by ethinylestradiol, the data for the pharmacokinetics of tadalafil and total methylcatechol metabolite following single- and multiple-dose 40 mg tadalafil administration are presented herein.

Results and Conclusions: Figure 2.7.2.5 and Figure 2.7.2.6 illustrate mean plasma concentration-time profiles for tadalafil and total methylcatechol metabolite, respectively, following once-daily administration of 40 mg tadalafil Days 1 and 21.



Source: CSR LVHM, Figure LVHM.7.11

Figure 2.7.2.5. **Arithmetic mean (± SEM) plasma concentration-time profiles of tadalafil following single and multiple doses of 40 mg tadalafil coadministered with oral contraceptive on Days 1 and 21.**



Source: CSR LVHM, Figure LVHM.7.12

Figure 2.7.2.6. Arithmetic mean (± SEM) plasma concentration-time profiles of total methylcatechol metabolite following single and multiple doses of 40 mg tadalafil coadministered with oral contraceptive on Days 1 and 21.

The accumulation (approximately 1.3-fold) for both AUC(0-24) and C_{max} are similar to those previously described following once-daily dosing of 40 mg tadalafil alone to healthy male subjects (Study LVGZ) and consistent with that expected based upon a terminal $t_{1/2}$ of 15.8 hours with once-daily administration. The general similarity of accumulation ratios following 10- and 21-day daily administration, indicates an absence of time-dependent tadalafil pharmacokinetics. Given the broadly similar exposure estimates across the present study to those previously described (Study LVGZ), coadministration of oral contraceptive did not appear to influence tadalafil pharmacokinetics and any differences in exposure estimates of tadalafil across studies were <15% and within the variability reported.

2.7.2.2.2.3. Effect of Other Drugs on the Pharmacokinetics of Tadalafil

Bosentan is a dual endothelin receptor antagonist that was the first oral therapy for PAH. Since nitric oxide and endothelin pathways are distinct mechanisms in PAH, combination therapy may provide additional clinical benefit, especially as oral agents of both are available. A potential issue with this combination therapy is a pharmacokinetic interaction, as bosentan induces CYPs 2C9 and 3A4, and both bosentan and tadalafil are CYP3A4 substrates. Owing to this, the combination of bosentan with tadalafil also warranted investigation.

LVGZ **A Pharmacokinetic Interaction Study Between Tadalafil and Bosentan in Healthy Male Subjects**

The study design for Study LVGZ was described previously (Section 2.7.2.2.2.1). Only the data for the effect of 125 mg bosentan twice-daily on the pharmacokinetics of 40-mg tadalafil once-daily are presented here.

Results and Conclusions: Administration of bosentan with single 40-mg doses of tadalafil did not discernibly alter tadalafil exposure on Study Day 1 (Table 2.7.2.4); however, by Study Day 10 of multiple-dose administration of bosentan with tadalafil, mean CL_{ss}/F and V_Z/F_{ss} of tadalafil were increased by approximately 70% and 53%, respectively, and corresponding $t_{1/2}$ values were slightly reduced with no change in t_{max}. Hence, associated decreases in tadalafil AUC_τ (41.5%) and C_{max} (26.6%) were observed and reflected in reductions in the accumulation ratios compared to administration of tadalafil alone.

Table 2.7.2.4. Statistical Comparison of Primary Pharmacokinetic Parameters for Tadalafil following Tadalafil Administered Alone and with Bosentan

						Treatment Comparisons			
Day	Parameter (unit)	Treatment	N	Geometric LS Mean	95% CI	Pair	Ratio/ Difference	90% CI	p-value
1	AUC_τ (ng·h/mL)	A	14	8550	(7770, 9400)				
		C	14	8660	(7870, 9520)	C/A	1.013	(0.917, 1.118)	0.8218
	C_{max}(ng/mL)	A	14	609	(549, 676)				
		C	14	647	(583, 717)	C/A	1.061	(0.938, 1.201)	0.4080
	t_{max}(h) *	A	14	4.00	(3.00, 4.03)				
		C	14	4.00	(3.00, 4.03)	C-A	-0.03	(-1.00, 0.00)	0.6445
10	AUC_τ (ng·h/mL)	A	13	12000	(10800, 13400)				
		C	14	7050	(6330, 7850)	C/A	0.585	(0.553, 0.620)	<.0001
	C_{max}(ng/mL)	A	13	819	(738, 909)				
		C	14	601	(543, 666)	C/A	0.734	(0.680, 0.793)	<.0001
	t_{max}(h) *	A	13	4.00	(3.00, 4.02)				
		C	14	3.00	(3.00, 4.00)	C-A	-0.02	(-1.00, 0.00)	0.3789

Notes: Treatment A = Tadalafil 40 mg once-daily for 10 days.
Treatment C = Tadalafil 40 mg once-daily and Bosentan 125 mg twice-daily for 10 days.
* For t_{max} the median is reported with approximate CI (Hahn and Meeker 1991) and p-value from Wilcoxon Sign Rank test.
Estimates based on a mixed-effects model with fixed effects of sequence, period and treatment, and random effect of subject.
CI = confidence interval.
AUC_τ = $AUC_{(0-24)}$ (Calculated based on actual time).
Source: CSR LVGZ, Table LVGZ.7.5

2.7.2.2.2.4. Effect of Tadalafil on the Pharmacokinetics of Other Drugs

When coadministered with an oral contraceptive pill containing levonorgestrel and ethinylestradiol, 10-mg tadalafil did not affect ovulation, and there were no clinically significant changes in endocrine profiles (leutinizing hormone, estradiol, progesterone, and follicle stimulating hormone) compared to coadministration with placebo. Further, plasma levonorgestrel concentrations were essentially similar to concentrations following administration of the oral contraceptive alone; however, ethinylestradiol concentrations were increased ($C_{max,ss}$ by 53% and $AUC_{\tau,ss}$ by 18%) relative to concentrations for administration of the oral contraceptive alone, suggesting an increase in bioavailability of ethinylestradiol (Study H6D-EW-LVAG [LVAG]). Given that the prevalence of PAH tends to be higher in women than in men, coadministration of tadalafil with oral

contraceptives is possible, thus a further study (Study LVHM) was conducted to assess whether a 40-mg dose of tadalafil results in a clinically significant pharmacokinetic drug-drug interaction as described below.

LVHM **A Study to Investigate the Effect of Tadalafil on Oral Contraceptive Pharmacokinetics in Healthy Female Subjects**

This was a double-blind, placebo-controlled, 3-period, 2-sequence, randomized, crossover study in 26 healthy female subjects to assess the single- and multiple-dose pharmacokinetics of 40-mg tadalafil when coadministered with oral contraceptive. Subjects received oral contraceptive (Microgynon®) for 3 consecutive cycles, with 1 tablet taken daily for 21 days followed by a 7-day oral contraceptive washout interval. In the first cycle, subjects took oral contraceptive with 40-mg tadalafil or oral contraceptive with placebo. The second cycle was a tadalafil washout phase during which subjects received oral contraceptive alone. In the third cycle, subjects received the alternate treatment to that administered in the first cycle. Subjects took tadalafil or placebo once daily for 21 consecutive days, concomitantly with oral contraceptive. Poststudy assessments were performed approximately 7 to 10 days after the last dose of tadalafil or placebo.

Results and Conclusions: Administration of oral contraceptive with single 40-mg doses of tadalafil resulted in higher AUC(0-24) (54%) and C_{max} (90%) of ethinylestradiol; following multiple-doses of oral contraceptive with tadalafil for 21 days increases in both AUC(0-24) (26%) and C_{max} (70%) of ethinylestradiol were observed relative to oral contraceptive and placebo (Table 2.7.2.5).

Table 2.7.2.5. Statistical Comparison of the Pharmacokinetic Parameters of Ethinylestradiol following Single and Multiple Doses of Oral Contraceptive (30 μg Ethinylestradiol and 150 μg Levonorgestrel) Coadministered with 40 mg Tadalafil or Placebo on Days 1 and 21

Parameter of ethinylestradiol	Day	Ratio of geometric LS means (tadalafil:placebo)	90% CI for the ratio (tadalafil:placebo)
AUC(0-24) (pg.h/mL)	1	1.54	1.44, 1.65
	21	1.26	1.18, 1.34
AUC(0-24)[a] (pg.h/mL)	1	1.53	1.43, 1.64
	21	1.25	1.17, 1.33
AUC(0-8) (pg.h/mL)	1	1.66	1.54, 1.79
	21	1.39	1.30, 1.49
AUC(0-8)[a] (pg.h/mL)	1	1.65	1.53, 1.79
	21	1.39	1.30, 1.48
C_{max} (pg/mL)	1	1.90	1.71, 2.10
	21	1.70	1.58, 1.82
C_{min} (pg/mL)	1	1.29	1.18, 1.41
	21	1.07	1.00, 1.15
t_{max} (h)[b]	1	0	-0.500, 0.525
	21	-0.500	-1.00, -0.0500

[a] Excluding data for Subject 2
[b] Median of differences (tadalafil - placebo) and associated 90% CI for median of differences for t_{max}
LS = Least squares
CI = Confidence interval
Source: CSR LVHM, Figure LVHM.7.2

The increase in ethinylestradiol concentrations in the presence of tadalafil are mirrored by decreases in the ethinylestradiol-sulfate, notably during the first 8-hours following coadministration of oral contraceptive with tadalafil. Accordingly, systemic ethinylestradiol-sulfate exposure was reduced for both AUC(0-24) (62%) and C_{max} (55%) on Day 1 following coadministration of single-doses of oral contraceptive and tadalafil suggesting inhibition of gut sulfation of ethinylestradiol by tadalafil (Table 2.7.2.6). After 21 days of multiple-dose administration of oral contraceptive and tadalafil, similar reductions in both AUC(0-24) (71%) and C_{max} (63%) of ethinylestradiol-sulfate were observed.

Table 2.7.2.6. Statistical Comparison of the Pharmacokinetic Parameters of Ethinylestradiol-Sulfate following Single and Multiple Doses of Oral Contraceptive (30 μg Ethinylestradiol and 150 μg Levonorgestrel) Coadministered with 40 mg Tadalafil or Placebo on Days 1 and 21

Parameter of ethinylestradiol sulfate	Day	Ratio of geometric LS means (tadalafil:placebo)	90% CI for the ratio (tadalafil:placebo)
AUC(0-24) (pg.h/mL)	1	0.381	0.325, 0.446
	21	0.285	0.242, 0.335
C_{max} (pg/mL)	1	0.445	0.387, 0.511
	21	0.367	0.330, 0.408
C_{min} (pg/mL)	1	0.610	0.531, 0.701
	21	0.375	0.341, 0.412
t_{max} (h)[a]	1	-0.483	-0.992, 0.0333
	21	-0.500	-1.00, 0

[a] Median of differences (tadalafil - placebo) and associated 90% CI for median of differences for t_{max}

LS = Least squares

CI = Confidence interval

Source: CSR LVHM, Figure LVHM.7.4

There was no statistically significant effect of tadalafil on levonorgestrel pharmacokinetics following single- and multiple-dose oral contraceptive administration. The 90% CI for the geometric least squares (LS) mean ratios for AUC and C_{max} were fully contained within the pre-defined limits of 0.80 to 1.25 and 0.70 to 1.43 for AUC and C_{max}, respectively (Table 2.7.2.7).

Table 2.7.2.7. Statistical Comparison of the Pharmacokinetic Parameters of Levonorgestrel following Single and Multiple Doses of Oral Contraceptive (30 μg Ethinylestradiol and 150 μg Levonorgestrel) Coadministered with 40 mg Tadalafil or Placebo on Days 1 and 21

Parameter of levonorgestrel	Day	Ratio of geometric LS means (tadalafil:placebo)	90% CI for the ratio (tadalafil:placebo)
AUC(0-24) (pg.h/mL)	1	0.890	0.820, 0.967
	21	1.02	0.961, 1.08
C_{max} (pg/mL)	1	0.828	0.752, 0.912
	21	1.02	0.969, 1.08
C_{min} (pg/mL)	1	0.916	0.823, 1.02
	21	0.994	0.925, 1.07
t_{max} (h) [a]	1	0.250	-0.250, 0.750
	21	-0.00833	-0.417, 0.250

[a] Median difference (tadalafil - placebo) and associated 90% CI for t_{max}

LS = Least squares

CI = Confidence interval

Source: CSR LVHM, Figure LVHM.7.6

LVGZ A Pharmacokinetic Interaction Study Between Tadalafil and Bosentan in Healthy Male Subjects

The study design for Study LVGZ was described previously (Section 2.7.2.2.2.1). Only the data for the effect of 40-mg tadalafil once-daily on the pharmacokinetics of 125-mg bosentan twice daily are presented here.

Results and Conclusions: Coadministration of tadalafil and bosentan (Study Day 1) did not discernibly alter exposure to bosentan (Table 2.7.2.8) or that of its metabolites, with any marginal difference (<20%) contained within the variability (29%) of the estimates and, thus, not clinically meaningful. Likewise, bosentan exposure was essentially similar on Study Day 10 when administered alone or with tadalafil.

Table 2.7.2.8. Statistical Comparison of Primary Pharmacokinetic Parameters for Bosentan following Bosentan Administered Alone and with Tadalafil

						Treatment Comparisons			
Day	Parameter (unit)	Treat-ment	N	Geometric LS Mean	95% CI	Pair	Ratio/ Difference	90% CI	p-value
1	AUC_{τ}(ng·h/mL)	B	14	7460	(5960, 9330)				
		C	14	8080	(6460, 10100)	C/B	1.084	(0.923, 1.272)	0.3867
	C_{max}(ng/mL)	B	14	1870	(1500, 2330)				
		C	14	2010	(1610, 2500)	C/B	1.075	(0.925, 1.250)	0.4065
	t_{max}(h) *	B	14	3.50	(3.00, 4.05)				
		C	14	3.00	(2.02, 5.00)	C-B	0.00	(-1.00, 0.00)	0.5898
10	AUC_{τ}(ng·h/mL)	B	14	4670	(3770, 5780)				
		C	14	5260	(4250, 6510)	C/B	1.126	(1.020, 1.243)	0.0546
	C_{max}(ng/mL)	B	14	1180	(918, 1520)				
		C	14	1410	(1100, 1820)	C/B	1.195	(1.054, 1.356)	0.0275
	t_{max}(h) *	B	14	4.02	(3.00, 5.00)				
		C	14	3.00	(3.00, 4.02)	C-B	-0.99	(-1.03, 0.00)	0.2041

Notes: Treatment B = Bosentan 125 mg twice-daily for 10 days.
Treatment C = Tadalafil 40 mg once-daily and Bosentan 125 mg twice-daily for 10 days.
* For Tmax the median is reported with approximate CI (Hahn and Meeker 1991) and p-value from Wilcoxon Sign Rank test.
Estimates based on a mixed-effects model with fixed effects of sequence, period and treatment, and random effect of subject.
CI = confidence interval.
$AUC\tau = AUC_{(0\text{-}12)}$ (Calculated based on actual time).
Source: CSR LVGZ, Table LVGZ.7.15

LVHL **A Study to Investigate the Effect of Tadalafil on the Steady-State Pharmacokinetics of Digoxin in Healthy Subjects**

Owing to the clinical utility of digoxin in PAH patients and its use as a probe involving P-gp, a randomized, open-label, single sequence study was conducted in 20 healthy subjects (14 males and 6 females) 18 to 57 years of age to assess the potential for a pharmacokinetic interaction between tadalafil and digoxin. Subjects received 2 loading doses of 0.5-mg digoxin (a total of 1.0 mg on Day 1) on Study Day 1 and single daily doses of 0.25-mg digoxin for the next 16 days (Study Days 2 through 17). Single daily doses of 40-mg tadalafil were coadministered with digoxin for 10 days (Study Days 8 through 17).

Results and Conclusions: Though digoxin $AUC_{\tau,ss}$ and $C_{max,ss}$ values were reduced by 10% and 5%, respectively, during daily coadministration with 40-mg tadalafil, the 90% CI for the ratio of the geometric LS mean were each fully contained within the prespecified interval of 0.80-1.25. Similarly, geometric mean $C_{min,ss}$ values were 14% lower when digoxin was given in combination with tadalafil, compared to digoxin alone, although the 90% CI for the ratio of geometric LS mean were within the 0.80 to 1.25 intervals. The absence of a drug interaction when digoxin is taken in combination with 40-mg tadalafil can therefore be concluded.

2.7.2.2.2.5. Population Pharmacokinetics and/or Population Pharmacokinetics/Pharmacodynamics

LVGY **A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of the Phosphodiesterase Type 5 (PDE5) Inhibitor Tadalafil in the Treatment of Patients with Pulmonary Arterial Hypertension**

Study LVGY was a multicenter, randomized, double-blind, placebo-controlled, parallel-design study to evaluate the efficacy and safety of 2.5, 10, 20, and 40 mg tadalafil taken once daily in subjects with PAH. Primary efficacy was measured by the unencouraged 6-minute walk test conducted at baseline and Weeks 4, 8, 12, and 16. Additionally, pharmacokinetic samples were collected at Weeks 4, 8, 12, and 16 for quantitation of tadalafil concentrations. The pharmacokinetic analysis included 1102 concentration observations from 305 subjects administered tadalafil with 1827 walk-test records from 389 subjects, including those receiving placebo, incorporated in the pharmacodynamic analysis dataset.

Pharmacokinetic Modeling

Pharmacokinetic, demographic, and clinical laboratory data were analyzed using population-based techniques. Table 2.7.2.9 provides the population pharmacokinetic parameter and variability estimates generated by the final model. The pharmacokinetic data obtained after once-daily dosing of tadalafil dosing was best described by a one-compartment model with a rapid first-order absorption rate (0.84 h^{-1}). The typical

estimate (% standard error of the estimate [SEE]) for CL/F was 1.59 L/h (5.0%) for subjects not receiving concomitant bosentan with a V/F of 79.7 L (6.7%). All parameters were estimated with adequate precision (%SEE below 22%).

Table 2.7.2.9. Pharmacokinetic and Covariate Parameter Estimates for Final Population Model of Tadalafil

Parameter Description	Population Estimate (%SEE)	Interindividual Variability (%SEE)
Rate of absorption		
Parameter for k_a (h^{-1})	0.84 (12.6)	---
Clearance[a]		
Parameter for CL/F (L/h)	1.59 (5.0)	48.6% (12.1)
Effect of concomitant bosentan on CL/F (L/h)	1.20 (10.8)	
Volume of distribution		
Parameter for V/F (L)	79.7 (6.7)	51.7% (21.9)
Bioavailability		
Parameter for F	1 (fixed)	---
Relative F for 40-mg treatment	0.65 (5.3)	---
Residual error (ratio of additive to proportional RV[b])	25.5 (41.6)	
Residual error (proportional)	0.0685 (8.7)	

Abbreviations: CL/F = apparent clearance; F = bioavailability fraction; k_a = absorption rate constant; RV = residual variability; %SEE = percent standard error of the estimate; V/F = apparent volume of distribution.

[a] Individual CL/F = 1.59 + 1.2 (BOS) where BOS = 0 when no concomitant bosentan use is reported and BOS = 1 for those receiving concomitant bosentan.

[b] Residual variability was estimated to range from 71.7 %CV to 26.2 %CV at predicted concentrations ranging from 10 ng/mL to 2000 ng/mL.

Source: LVGY Population PK/PD Report, Table LVGY.9.7

Subject factors examined as potential covariates (Table 2.7.2.10) were prospectively defined based upon previous population pharmacokinetic analyses (Studies LVCE, LVDI, LVFP) and disease-related characteristics.

Table 2.7.2.10. Subject Factors Assessed in the Population Pharmacokinetic Analysis

Categorical
Sex
Ethnicity
History of cardiovascular disease (CAD1, CAD2)
PAH history
Tadalafil dose, mg
Concomitant medications – bosentan, digoxin, warfarin[a]
Continuous
Age, years
Time on therapy, hours
Body weight, kg
PAH duration, years
Alanine aminotransferase (ALT), U/L
Aspartate aminotransferase (AST), U/L
Total bilirubin (TBIL), µmol/L
Creatinine clearance (CrCL), mL/min
PAH duration, years
Total serum protein, g/L

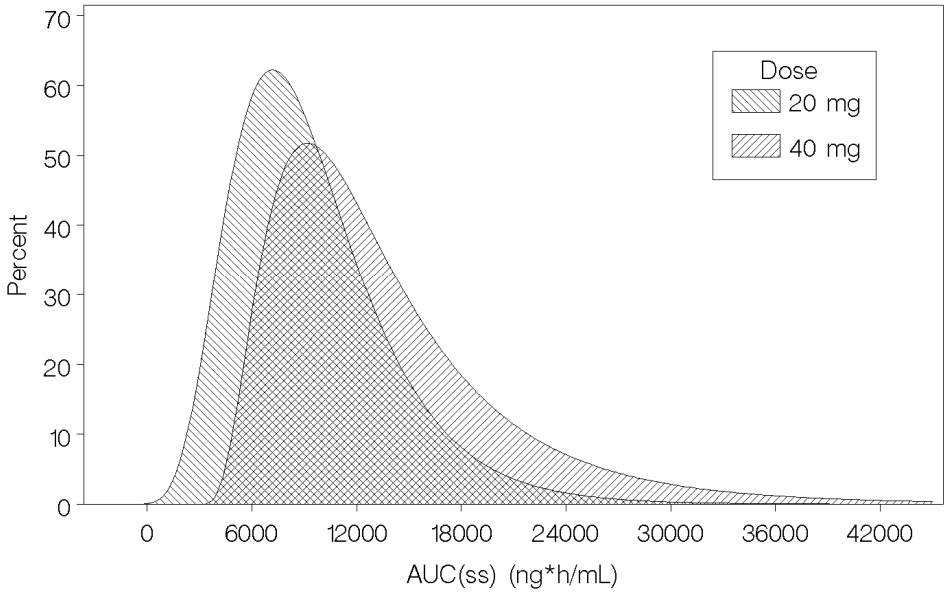
Abbreviation : PAH = pulmonary arterial hypertension.

[a] Time-varying characteristics were measured during study visits at Weeks 4, 8, 12, and 16.

Source LVGY Population PK/PD Report, Table LVGY.8.1

Systemic exposure to tadalafil was not influenced by cardiovascular conditions, gender, ethnicity, PAH history or duration, creatinine clearance, total serum protein, weight, warfarin, or digoxin, thereby suggesting that tadalafil can be administered without regard to these factors.

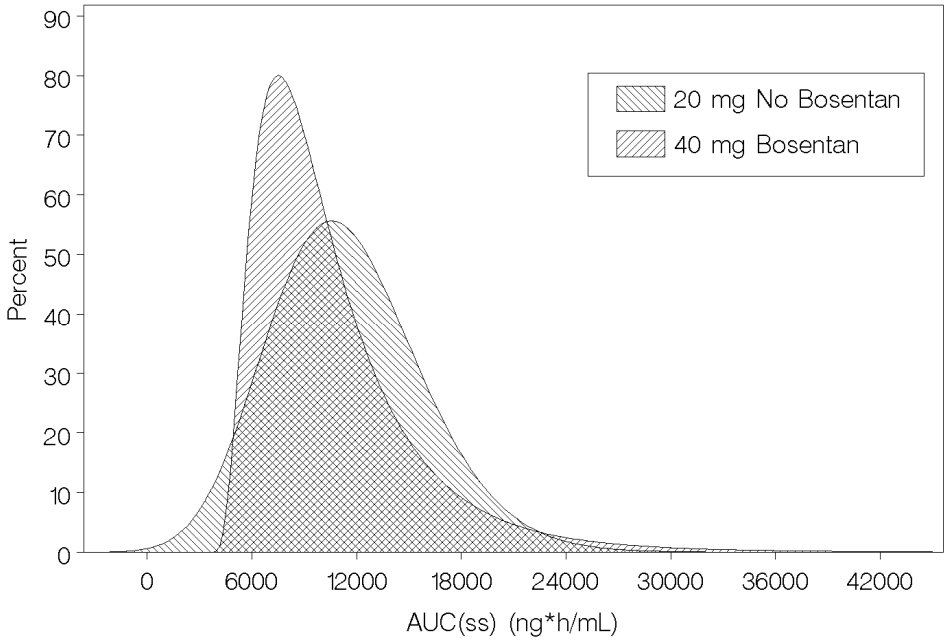
The parameter estimate for the relative bioavailability of the 40-mg dose was 0.65, indicating a reduction in bioavailability of 35% (95% CI: 28.6% - 42.0%) for the 40-mg dose when compared to lower tadalafil doses (2.5, 10, and 20 mg) studied in this trial. Furthermore, a bioequivalence assessment of the individual AUC_{ss} values comparing the 40-mg to the 20-mg dose group reveals a geometric mean ratio (90% CI) of 1.48 (1.30, 1.68). When this assessment is stratified by concomitant bosentan use, similar results are obtained whereby, in subjects receiving concomitant bosentan, a 2-fold change in dose from 20-mg to 40-mg results in a 1.41-fold (1.22, 1.64) increase in systemic exposure and in subjects not receiving concomitant bosentan, a 1.53-fold (1.28, 1.82) increase in exposure is observed. Thus, due to the lack of dose proportionality between 20 mg and 40 mg, a nominal dose of 40 mg provides exposures approximating a 30-mg (90% CI: 26, 34 mg) dose. Furthermore, approximately 81% of the tadalafil exposures predicted following 40 mg once-daily administration were within those estimated following 20 mg (Figure 2.7.2.7).



Source: LVGY Population PK/PD Report, Figure LVGY.9.7

Figure 2.7.2.7. Probability distributions of individual predicted tadalafil AUC_{ss} for subjects administered 20 mg and 40 mg tadalafil.

A strong relationship between tadalafil clearance and concomitant bosentan use was observed in the population analysis where 51% of subjects were receiving bosentan. Predicted tadalafil clearance increased linearly from 1.59 to 2.79 L/h in those subjects receiving bosentan resulting in a predicted median AUC (range) following 40-mg tadalafil alone of 14825.50 ng × hr/mL (6195 – 43426 ng × hr/mL) and that after coadministration with bosentan being 9599.95 ng × hr/mL (5059 – 23687 ng × hr/mL) representing a decrease of approximately 35% in the median AUC_{ss} with bosentan. Additionally, 97% of the predicted tadalafil exposures for those receiving 40-mg tadalafil with concomitant bosentan are within the 5th to 95th percentiles of the distribution of exposures in subjects receiving 20-mg tadalafil alone (Figure 2.7.2.8) demonstrating appreciable concordance amongst these subject groups, indicating that tadalafil exposures are comparable between bosentan naive subjects receiving 20 mg tadalafil and subjects coadministered tadalafil 40 mg with bosentan.



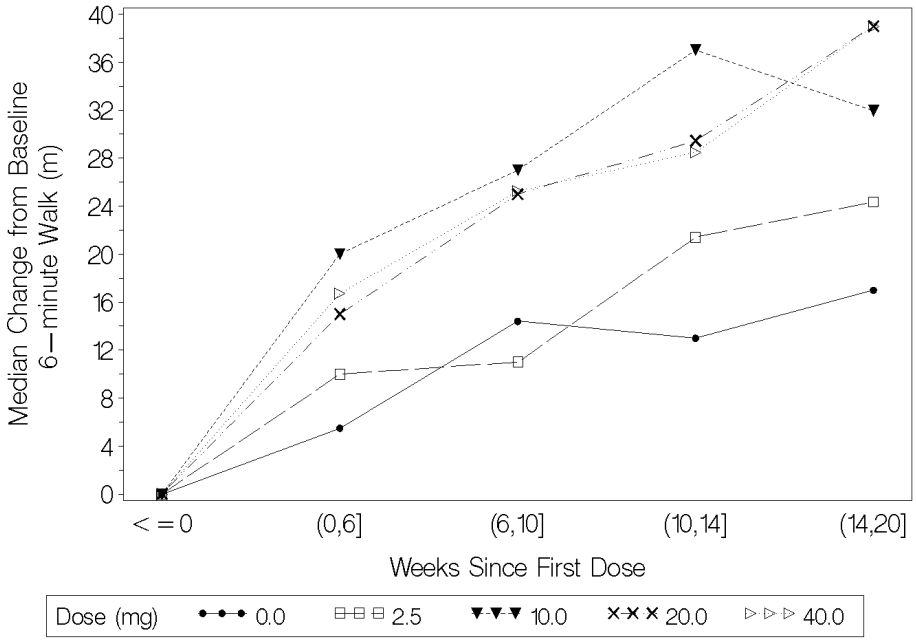
Source: LVGY Population PK/PD Report, Figure LVGY.9.13

Figure 2.7.2.8. Probability distributions of individual predicted tadalafil AUC_{ss} for subjects receiving 40 mg tadalafil with concomitant bosentan and those receiving 20 mg tadalafil alone.

Pharmacokinetic/Pharmacodynamic Modeling

Population-based mixed-effects modeling was used to characterize subject factors influencing 6-minute walk response to tadalafil incorporating tadalafil exposure measures (AUC_{ss}, C_{max}, and C_{min}) derived from the final population PK model. For subjects who received active drug (n = 307), exposure measures were the same for all study visits, as no time-varying covariates were identified that influenced the constancy of apparent clearance over the duration of treatment. All exposure measures were assigned a value of 0 for subjects who received placebo. The PK/PD analysis included 1827 records from 389 subjects (86 male and 303 female) administered placebo (n = 82) or tadalafil 2.5 mg (n = 77), 10 mg (n = 77), 20 mg (n = 78), or 40 mg (n = 75) once-daily.

Figure 2.7.2.9 illustrates the observed median change from baseline in 6-minute walk distance for each treatment, unadjusted for placebo. The placebo and tadalafil 2.5-mg dose groups have comparable increases in median walk distance over time profiles; whereas, the 10-, 20-, and 40-mg dose groups have greater median increases at all time-points. Similar 6-minute walk distances were observed at the endpoint of Study LVGY for subjects receiving 20-mg and 40 mg tadalafil and were congruent with the dose-dependent increases in the change in 6-minute walk distance from baseline with increasing treatment duration, specifically for doses up to and including 20 mg tadalafil.



Source: LVGY Population PK/PD Report, Figure LVGY.9.17

Figure 2.7.2.9. Plot of median change from baseline in 6-minute walk versus weeks since first dose, stratified by tadalafil dose.

The PK/PD parameter and variability estimates were generated by the final model for subjects receiving placebo and active treatment. For placebo subjects, no time-course of 6-minute walk response was discerned; however, a linear function of age and baseline 6-minute walk best described 6-minute distance (Equation 1). For subjects receiving active tadalafil treatment, an E_{max} model best described the time-course of 6-minute walk response with age and tadalafil AUC_{ss} influencing E_{max}, and baseline 6-minute walk, PAH etiology, and concomitant calcium channel blocker therapy significantly affecting T_{50} (Equation 2). For all subjects, WHO class was a significant predictor of the baseline 6-minute walk parameter, with those having WHO Class III and IV having a 50 meter reduction in baseline walk measures compared to those with Class I and II. All parameters were estimated with adequate precision, generally with a %SEE of less than 45%. The magnitude of the intersubject variability for baseline 6-minute walk (19.29 %CV) decreased and E_{max} (SD of 62.21 meters) was relatively unchanged as compared to the base structural model.

[Equation 1]

$$\text{Placebo 6-Minute Walk} = 321 + 50.4 \times WHO2 + 186 \times \left(\frac{BaselineWalk}{363}\right) - 150 \times \left(\frac{Age}{54.4}\right)$$

where WHO2 = 1 for WHO Class I or II and WHO2 = 0 for WHO Class III or IV.

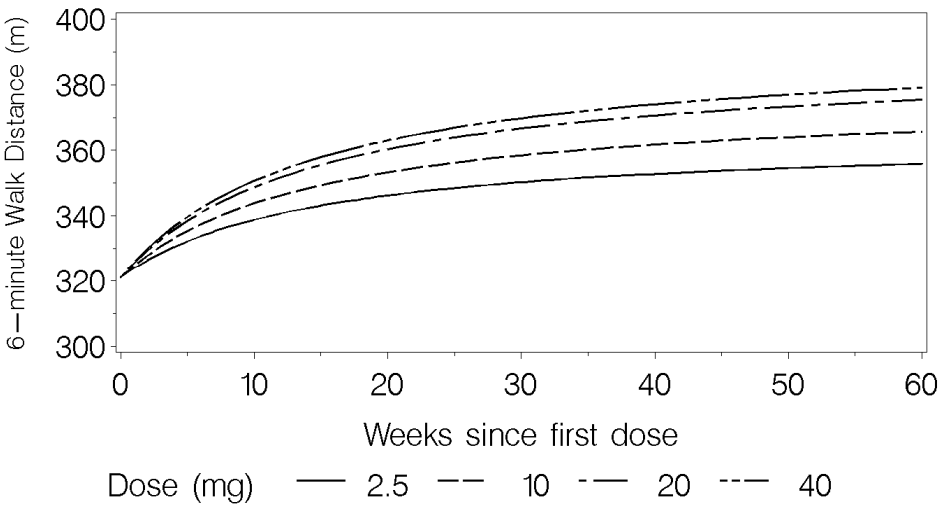
[Equation 2]

$$\text{Active Tadalafil 6-Minute Walk} = (321 + 50.4 \times \text{WHO2}) + \frac{\left[\left(60.9 \times \left(\frac{\text{AUC}_{ss}}{5955.3}\right)^{0.225} - 1.96 \times (\text{Age} - 53.9)\right) \times \text{WSFD}\right]}{\left(14.2 \times \left(\frac{\text{BaselineWalk}}{359}\right)^{1.51} + 14 \times \text{PAHC} - 3.11 \times \text{PAHO} - 5.45 \times \text{CCB}\right) + \text{WSFD}}$$

where WHO2 = 1 for WHO Class I or II and WHO2 = 0 for WHO Class III or IV; PAHC = 1 for PAH related to collagen disorders and PAHC = 0 otherwise; PAHO = 1 for other PAH and PAHO = 0 for idiopathic and related to collagen disorders; CCB = 1 for those receiving concomitant calcium channel blockers and CCB = 0 when no concomitant calcium channel blockers were reported; WSFD = week since first tadalafil dose.

Source: LVGY Population PK/PD Report, Table LVGY.9.16

The model predicts for subjects receiving tadalafil treatment, a typical baseline 6-minute walk of 321 meters with a typical maximum response of 61 meters assuming the overall median AUC_{SS} of 5955 ng*h/mL, and 14 weeks of treatment to achieve 50% of this maximal response (Figure 2.7.2.10). Increasing age decreased overall response by 1.96 meters/year above 53.9 years of age.



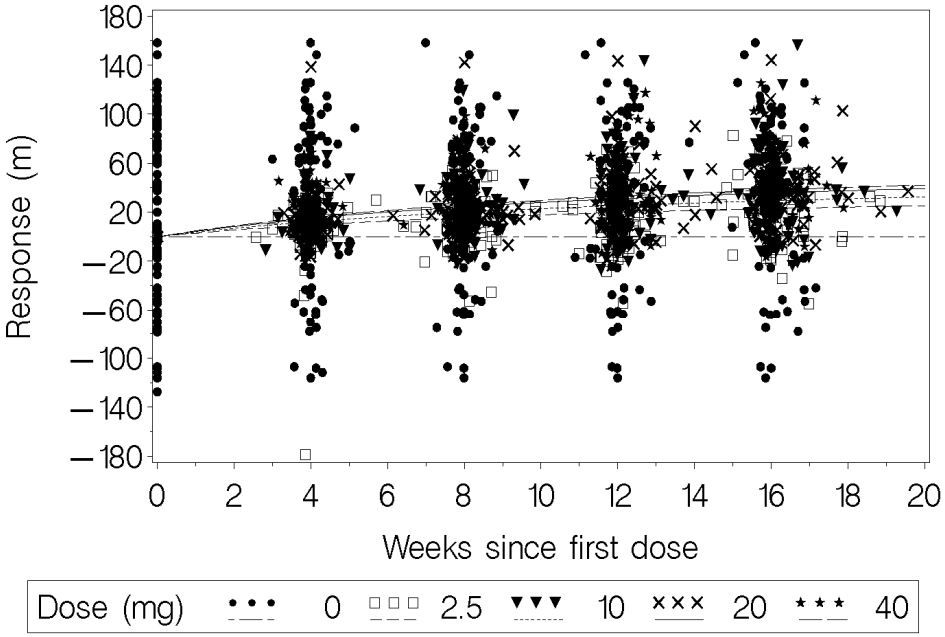
Age and baseline 6−minute walk were fixed to the tadalafil population median values.
The model−predicted lines assume idiopathic PAH history and no calcium channel blockers.
Source: LVGY Population PK/PD Report, Figure LVGY.9.25

Figure 2.7.2.10. Population predicted 6-minute walk versus weeks since first dose stratified by tadalafil dose from the final pharmacokinetic/pharmacodynamic model.

Although several covariates were found to be significant predictors of T_{50} (PAH history, baseline 6-minute walk, and concomitant calcium channel blockers), these covariates affected only the time at which 50% of the maximal 6-minute response would be achieved and did not alter the predicted extent of response. Six-minute walk response was not influenced by duration of PAH, weight, gender, ethnicity, or concomitant digoxin or bosentan, suggesting that response to tadalafil is not altered with regard to these factors.

Following 16 weeks of treatment with tadalafil, the model-predicted increase in 6-minute walk response is greater than 30 meters for 20- and 40-mg doses, irrespective of bosentan use whereas, lower doses generally resulted in an estimated increase in exercise capacity of 20-30 meters with no discernible response for those receiving placebo (Figure 2.7.2.11). Overall, irrespective of bosentan use, at 16 weeks of treatment the model-predicted increase in 6-minute walk from baseline is predicted to be 35.63 (30.49, 39.57) and 38.09 (33.52, 43.20) meters for 20 and 40 mg tadalafil, respectively, assuming the median (10th and 90th percentiles) AUC_{ss}. At the end of the treatment period (Week 16), the model-predicted increase in 6-minute walk from baseline is predicted to be 33.32 and 37.43 meters for 20-mg tadalafil assuming the median AUC_{ss} with and without concomitant bosentan, respectively (Table 2.7.2.11). Comparatively, following 16 weeks of 40-mg daily tadalafil, the increase in 6-minute walk from baseline is estimated to be 35.92 meters with bosentan and 39.61 meters without concomitant bosentan (Table 2.7.2.11). Moreover, despite PAH etiology impacting T_{50} whereby subjects with

idiopathic PAH having faster responses (approximately 11 weeks) compared to those with collagen vascular disorders (approximately 28 weeks), any difference in predicted 6-minute walk response based on median exposures associated with tadalafil doses of 20- and 40-mg are less than 2 meters irrespective of bosentan use at 16 weeks of treatment.



Source: LVGY Population PK/PD Report, Figure LVGY.9.37

Figure 2.7.2.11. **Individual increase in 6-minute walk versus weeks since first dose stratified by tadalafil dose with typical value predicted curves from the final pharmacokinetic /pharmacodynamic model overlaid.**

Table 2.7.2.11. Week 16 Model-Predicted 6-minute Walk Response Assuming the Median, 10th, and 90th Percentiles of AUC_{ss} at Each Dose

Dose	No Bosentan		Concomitant Bosentan	
	AUC_{ss} (ng × h/mL)[a]	Increase in 6-minute walk (m)	AUC_{ss} (ng × h/mL)[a]	Increase in 6-minute walk (m)
2.5 mg	1950.4 (913.4 – 3737.6)	25.10 (21.16 – 29.05)	1092.1 (680.46 – 2128.0)	22.03 (19.80 – 25.60)
10 mg	6936.9 (2870.4 – 10898.0)	33.39 (27.38 – 36.96)	2902.8 (2193.5 – 4279.0)	27.45 (25.77 – 29.95)
20 mg	11524.5 (6179.6 – 15449.0)	37.43 (32.53 – 39.98)	6874.60 (4390.0 – 10595.0)	33.32 (30.13 – 36.73)
40 mg	14825.5 (10017.0 – 26792.0)	39.61 (36.27 – 45.26)	9599.9 (5906.3 – 17306.0)	35.92 (32.21 – 41.02)

Abbreviation: AUCss = area under the concentration-time curve at steady state.

[a] Median (10th – 90th percentile)

Source: LVGY Population PK/PD Report, Table LVGY.9.20

In summary, it is concluded that subjects who benefited most from tadalafil treatment received doses of at least 20 mg tadalafil once-daily, irrespective of the pharmacokinetic influence of bosentan and other disease or subject-specific factors.

2.7.2.3. Comparison and Analysis of Results across Studies

2.7.2.3.1. General Pharmacokinetic Properties

2.7.2.3.1.1. Single and Multiple-Dose Pharmacokinetics in Healthy Subjects Following 40 mg Administration

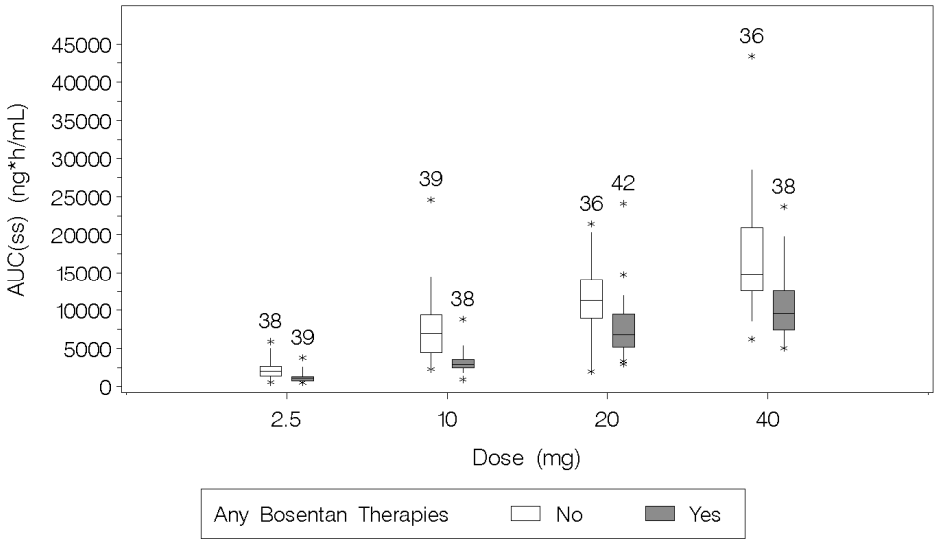
Maximum plasma concentrations of tadalafil were generally achieved at approximately 4 hours after dosing, irrespective of single or multiple-dose administration. Plasma concentrations of total methylcatechol continuously increased up to 24 hours postdose on Day 1, reflecting a formation-dependent process. Pharmacokinetics of tadalafil and total methylcatechol following multiple-dose administration were consistent with those observed after single-dose administration, indicating an absence time-dependent pharmacokinetics of both tadalafil and total methylcatechol metabolite. The geometric mean (range) apparent plasma clearance of tadalafil is 3.39 (2.32 to 5.17) L/hour with modest variability (23.9%) following multiple-dose daily 40 mg administration. Application of a relative bioavailability of 0.649 for a 40-mg dose to the apparent clearance estimate of 3.39 L/h results in a value of 2.19 L/h, which is congruent with clearance estimates in healthy subjects receiving 20 mg, and summarized in previous applications (Study LVGZ and LVGY Population PK/PD Report). The estimates of tadalafil accumulation (approximately 1.3-fold for both AUC_{τ} and C_{max}) are comparable

to that expected (1.54-fold) given the terminal half-life of 15.8 hours. Tadalafil and total methylcatechol systemic exposure (AUC and C_{max}) was similar across Days 5 and 10, suggesting that steady-state is likely achieved by Day 5. The average metabolic ratio, based upon AUC_{ss} ($AUC_{ss,\ metabolite}/AUC_{ss,\ parent}$) was 1.25. The intrasubject variability estimated for AUC and C_{max} were 14.3% and 18.1%, respectively, following 40-mg multiple-dose administration, indicating consistent exposure from one occasion to the next.

2.7.2.3.1.2. Population Pharmacokinetics in Subjects with PAH and ED

A one-compartment model best described the pharmacokinetics of tadalafil in subjects with PAH. The population estimate for CL/F and V/F was 1.59 L/h and 79.7 L, respectively. Systemic exposure to tadalafil was not influenced by cardiovascular conditions, gender, ethnicity, PAH history or duration, creatinine clearance, total serum protein, weight, warfarin, or digoxin, thereby suggesting that tadalafil can be administered without regard to these factors. Bioavailability and concomitant bosentan therapy produced significant covariate effects in the population pharmacokinetic analysis.

Due to a statistically significant decrease in bioavailability with 40-mg once daily doses as compared to lower doses, a 2-fold change in dose from 20 to 40 mg results in a 1.48-fold increase in exposure (Figure 2.7.2.12). Apparent oral clearance of tadalafil was increased by 75% with concomitant bosentan, resulting in a decrease in systemic exposure to tadalafil of 35% for subjects receiving 40-mg tadalafil with concomitant bosentan therapy as compared to those receiving 40-mg tadalafil alone.



Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th to 95th percentiles.
Asterisks show data points outside this range. The number of observations is above each box.

Source: LVGY Population PK/PD Report, Figure LVGY.9.10

Figure 2.7.2.12. Individual predicted AUC_{SS} versus tadalafil dose stratified by subjects not receiving concomitant bosentan.

Similar to the results in the clinical evaluation of subjects with PAH, the pharmacokinetics of tadalafil in subjects with ED receiving daily doses of 2.5 and 5 mg were best described by a one-compartment model and no patient-specific factor warranting clinical consideration of a dosage adjustment was identified in Study LVFP. The typical values and 95% confidence interval calculated from the final model and parameter sensitivity analysis from Study LVFP were compared with those generated in the Study LVGY analysis. Both the typical CL/F and V/F estimates from Studies LVFP and LVGY were broadly similar with any difference being <20% and unlikely to be clinically relevant (Table 2.7.2.12). As a dose range of 2.5 to 20 mg was principally investigated for the ED indication and as bosentan use is only expected in a PAH population, a 20 mg daily dose of tadalafil in the absence of concomitant bosentan administration was selected to further evaluate the pharmacokinetic comparability between subjects with ED and PAH. In this regard, the 95% CIs of the plasma concentration profiles generally demonstrate considerable overlap, indicating that systemic exposure to tadalafil in subjects with PAH is essentially similar to that in those with ED receiving equivalent doses and regimens (Figure 2.7.2.13).

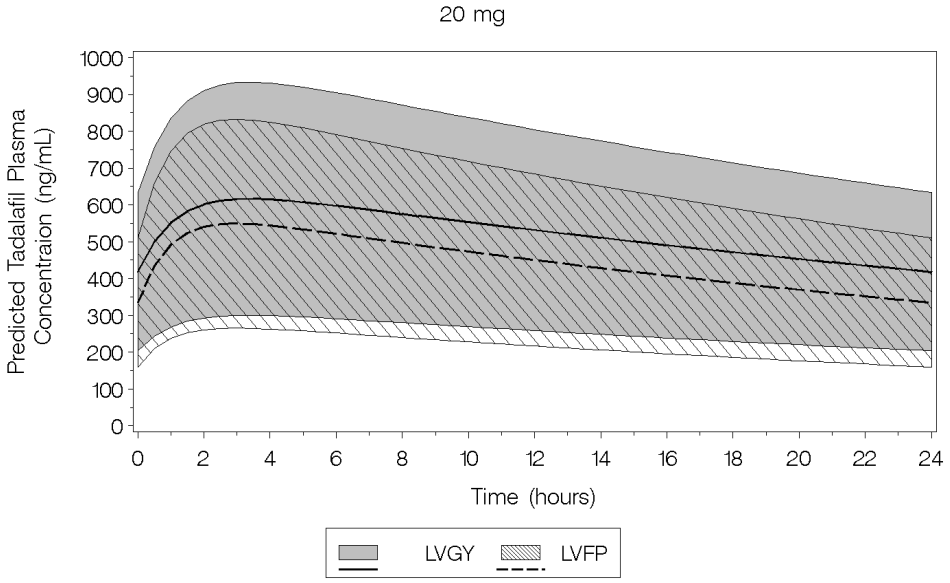
Table 2.7.2.12. Comparison of Parameter Estimates (95% CI) from Studies LVFP and LVGY

	k_a (h^{-1})	CL/F (L/h)	V/F (L)
Study LVFP	1.01 (0.758 – 1.34)	1.87 (1.70 – 2.08)	75.8 (65.8 – 88.3)
Study LVGY	0.844 (0.655 – 1.10)	1.59 (1.45 – 1.74)[a]	79.7 (70.9 – 90.9)

Abbreviations: CL/F = apparent clearance…

[a] Represents the estimate of apparent oral clearance in subjects not receiving concomitant bosentan.

Source: LVGY Population PK/PD Report, Table LVGY.9.19



The shaded regions represent the 95% confidence interval calculated using residual variability.
The solid and dashed lines represent the steady—state typical concentrations for 20 mg.

Source: LVGY Population PK/PD Report, Figure LVGY.9.31

Figure 2.7.2.13. Population predicted tadalafil concentrations versus time profiles with 95% confidence intervals following tadalafil once-daily 20 mg Administration in Subjects with ED (Study LVFP) Compared to those with PAH (Study LVGY).

In patients with pulmonary hypertension not receiving concomitant bosentan, the predicted median tadalafil exposure at steady-state following 40 mg was 14825.59 ng*h/mL and 26% higher when compared to those of healthy volunteers. There were no clinically relevant differences in mean C_{max} compared to healthy volunteers (Figure 2.7.2.14). The results suggest a potentially lower mean clearance of tadalafil in patients with pulmonary hypertension compared to healthy volunteers; however, the distribution of plasma concentrations observed in healthy subjects is within the 95% confidence interval of those with PAH and indicate that tadalafil systemic exposure is generally comparable in patients and healthy subjects receiving equivalent doses.

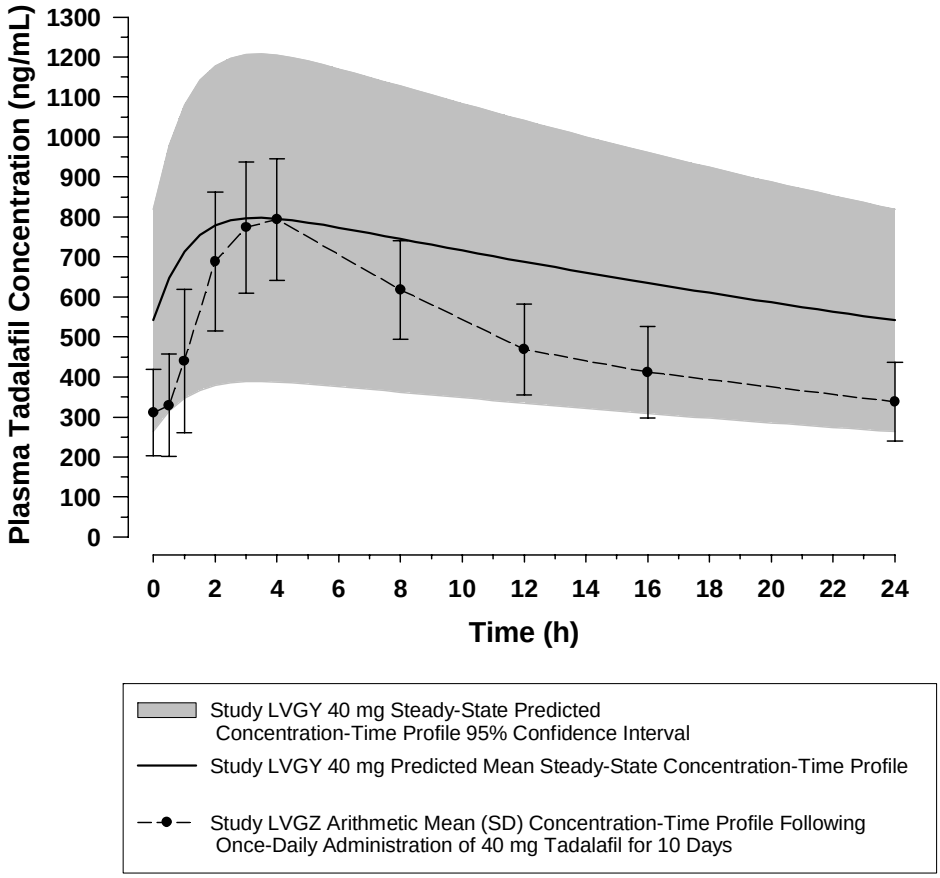


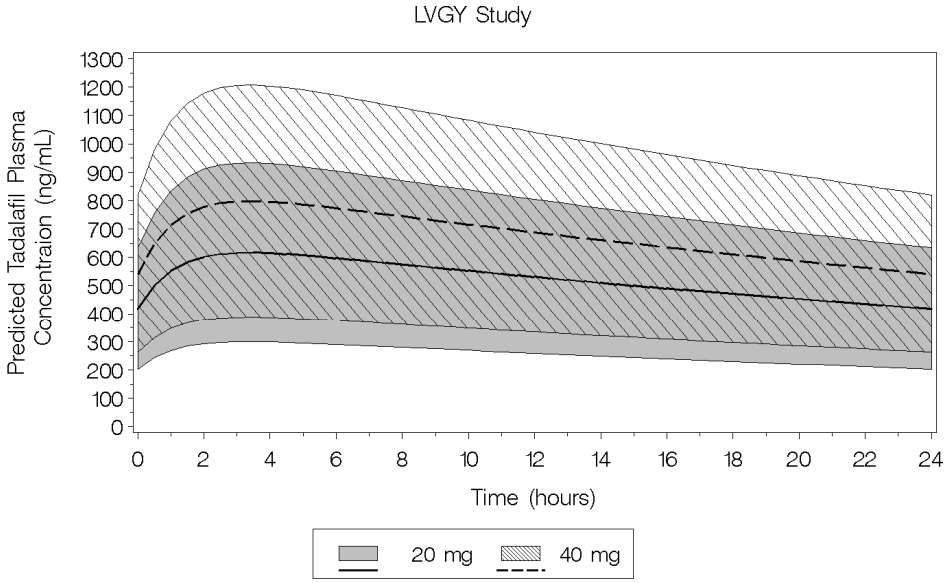
Figure 2.7.2.14. Tadalafil steady state concentration-time profile following daily dosing of 40 mg in subjects with PAH (Study LVGY) and healthy subjects (Study LVGZ).

2.7.2.3.1.3. Dose Proportionality

Over the dose range of 5 to 40 mg (Study LVCS), the regression coefficient estimates (slopes) (90% CI) of the AUC(0-∞) and C_{max} were 0.93 (0.89, 0.97) and 0.80 (0.76, 0.85), respectively. Thus, over the dose range of 5 to 40 mg, the AUC(0-∞) and C_{max} increased in a slightly less than dose proportional manner. Given the apparent absorption-rate limitations of tadalafil at the highest dose, the median t_{max} of 4 hours following 40 mg administration is modestly prolonged compared to doses of 20 mg or less; however, within the range of that reported following 20 mg single-dose administration. The intrasubject variability estimated from multiple-dose administration of 40 mg for AUC and C_{max} were 14.3% and 18.1%, respectively, and slightly less following multiple-dose administration, indicating consistent exposure from one occasion to the next.

Applying a confidence interval approach to the Study LVGY steady-state data and comparing the 40-mg to the 20-mg dose group reveals a geometric mean ratio (90% CI)

of 1.48 (1.30, 1.68). Thus, due to the lack of dose proportionality between 20 mg and 40 mg, a nominal dose of 40 mg provides exposures approximating a 30-mg (90% CI: 26, 34 mg) dose. When this assessment is stratified by concomitant bosentan use, similar results are obtained. The decrease in relative bioavailability of the 40-mg dose as compared to lower doses is independent of concomitant bosentan and comparable in both bosentan users and those receiving tadalafil alone. Furthermore, approximately 81% of the tadalafil exposures predicted following 40 mg once-daily administration were within those estimated following 20 mg, leading to considerable overlap in the population predicted concentration-time profiles (Figure 2.7.2.15).



The shaded regions represent the 95% confidence interval calculated using residual variability.
The solid and dashed lines represent the steady—state typical concentrations.

Source: LVGY Population PK/PD Report, Figure LVGY.9.6

Figure 2.7.2.15. Population predicted tadalafil concentrations versus time for 20- and 40-mg doses from Study LVGY with 95% confidence intervals.

2.7.2.3.2. Effect of Intrinsic Factors

As studies in special populations generally reflect tadalafil 10-mg single dose administration and doses of 40 mg were not specifically examined in support of the PAH indication, an assumption of linearity is applied to existing data as this would over-estimate exposures that are likely to be observed and constitutes a more conservative projection of anticipated exposure. Moreover, as the loss of strict dose-proportional pharmacokinetics appears to be attributable to rate-limited absorption rather than alterations to the intrinsic biotransformation of tadalafil, the presumption of linearity is scientifically appropriate.

2.7.2.3.2.1. Gender

Based upon the most recent examinations following 40 mg daily tadalafil administration, the individual tadalafil plasma concentration time profiles for females and males are essentially similar following single and multiple, once-daily doses of 40 mg tadalafil (Studies LVHC, LVGZ, and LVHM). The overlap in the distribution of AUCτ and C_{max} values for female and male subjects is apparent, with any mean difference being <10% and of no clinical relevance (Figure 2.7.2.16).

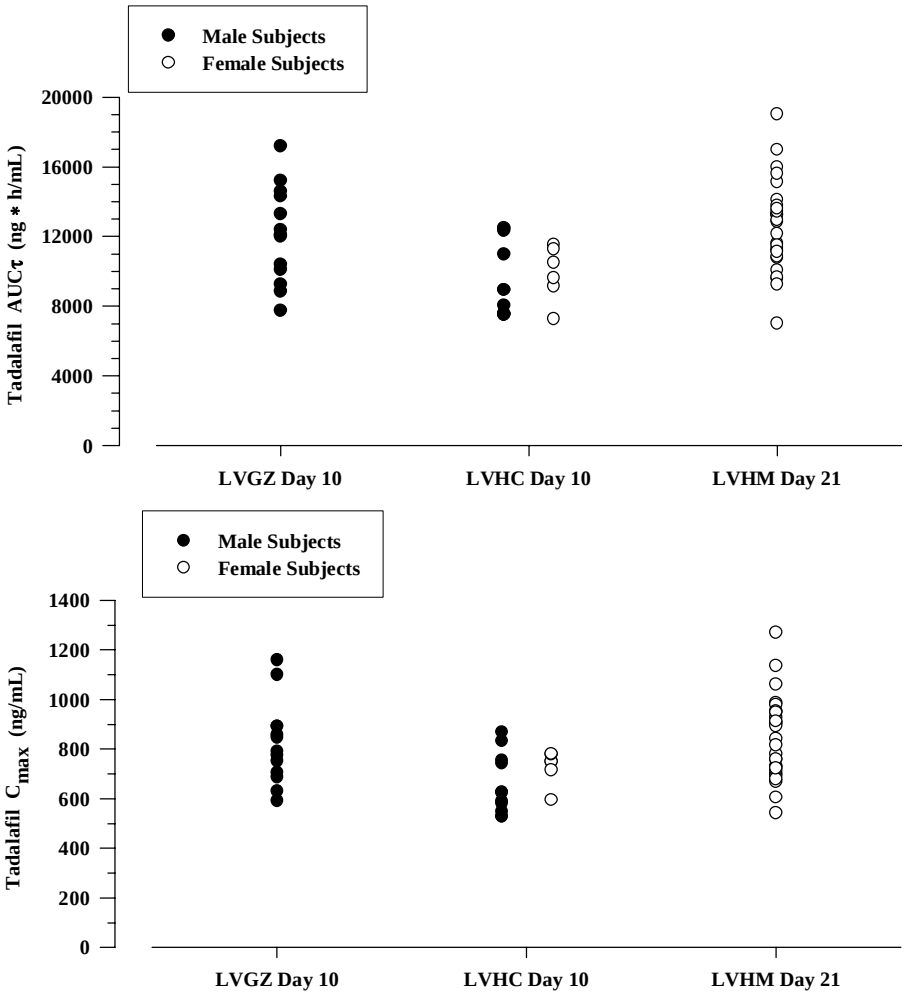


Figure 2.7.2.16. Individual comparisons of tadalafil AUCτ (upper panel) and C_{max} (lower panel) following once-daily dose administration of 40 mg tadalafil in Studies LVGZ, LVHC and LVHM.

Additionally, a population-based nonlinear mixed-effects model based upon prespecified statistical criteria including a clinically relevant change in CL/F (≥ 20%), was employed to evaluate the influence, if any, of gender on tadalafil disposition (LVGY Population PK/PD Report). Systemic exposure to tadalafil was not influenced by gender (Figure 2.7.2.17), no discrete montonic trend for increased exposures between males and females was discerned, with any median difference in CL/F being approximately 5% higher in

females and contained within the 5th to 95th percentiles of CL/F estimates of men. Given that females comprised approximately 77% of the Study LVGY population, gender would have likely been identified as a significant covariate if a clear pattern of increased (25%) exposures were differentiable from female and male subjects. The lack of significance of gender on tadalafil CL/F and hence, systemic exposure does not indicate a pharmacokinetic basis for specific dose adjustments based upon gender.

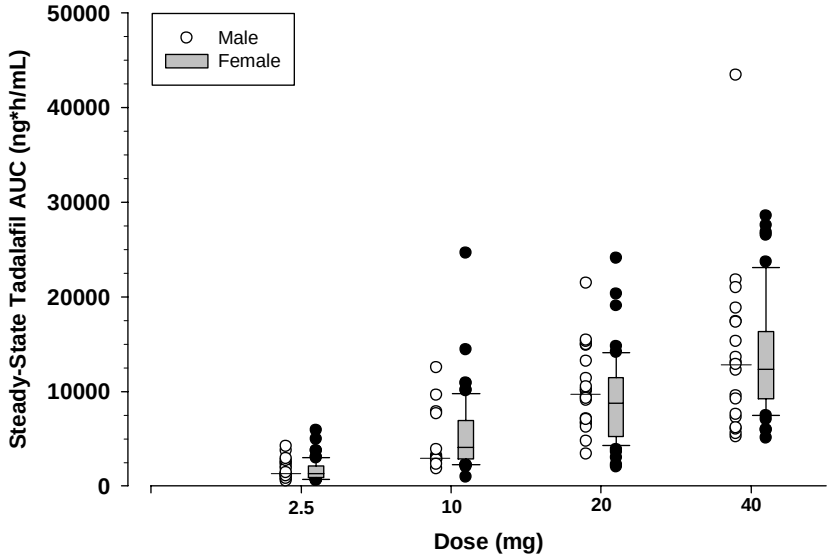


Figure 2.7.2.17. **Predicted tadalafil exposure across gender for subjects in Study LVGY receiving tadalafil 2.5-, 10-, 20-, or 40-mg daily doses.**

Additionally, in clinical studies of PAH (Studies LVGY and LVGX) (Section 2.7.4), the safety and tolerability of tadalafil is similar between male and female subjects and no exposure-limiting side effects have been observed in either population. Therefore, any minor exposure difference in males and females is not considered to be clinically relevant and recommended tadalafil dosing should be the same for men and women.

2.7.2.3.2.2. Ethnicity

The pronounced majority of subjects represented in the pharmacokinetic analysis of Study LVGY were Caucasian (79%), such that only limited data from those of different ethnicities were available; whereby no single ethnic group (African descent, Eastern Asian, Native American, or Other) represented >10% of the PAH subject population (LVGY Population PK/PD Report). Hence, assessment of any influence of ethnicity on tadalafil disposition was based on stratification by Caucasian and non-Caucasian with pharmacostatistical comparisons conducted to assess the influence of ethnicity on CL/F. No influence of ethnicity on tadalafil disposition was identified. For those geographical regions represented in the pharmacokinetic analysis and reflecting >2% (N=6) of the

population, no discrete pattern indicating appreciable differences in tadalafil exposures was observed (Figure 2.7.2.18).

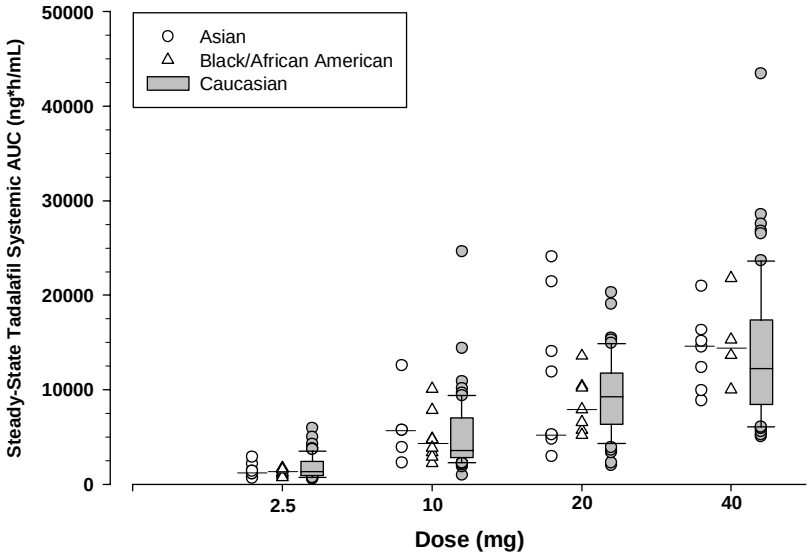
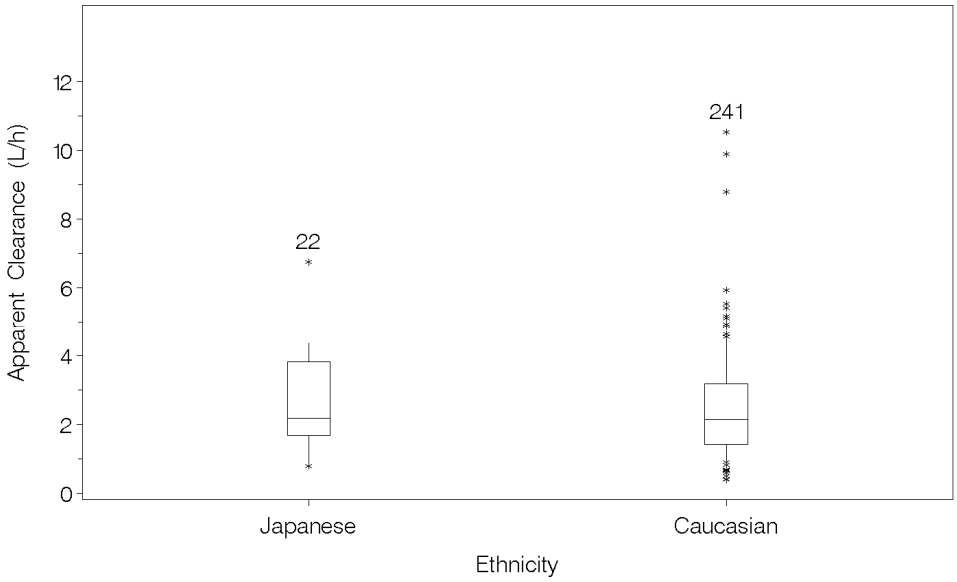


Figure 2.7.2.18. Predicted tadalafil exposure across ethnicity for subjects in Study LVGY receiving tadalafil 2.5-, 10-, 20-, or 40-mg daily doses.

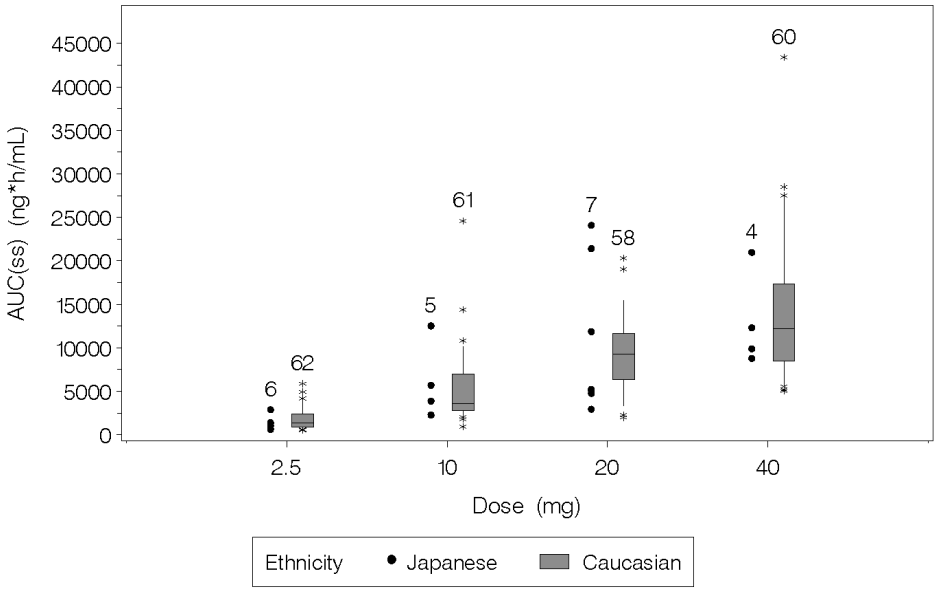
The similarity between pharmacokinetic parameters derived from Japanese (n=22) and Caucasian (n=241) subjects with PAH was further evaluated by comparing the distribution of the individual Bayesian estimates of CL/F (Figure 2.7.2.19) and resultant individual estimates of exposure (Figure 2.7.2.20) from Study LVGY. There was considerable overlap and no overt differences in CL/F, with >96% concordance, and tadalafil exposure between each ethnic group.



Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th to 95th percentiles.
Asterisks show data points outside this range. The number of observations is above each box.

Source: LVGY Population PK/PD Report, Figure LVGY.9.33

Figure 2.7.2.19. Individual tadalafil apparent clearance estimates versus Japanese and Caucasian ethnicity.



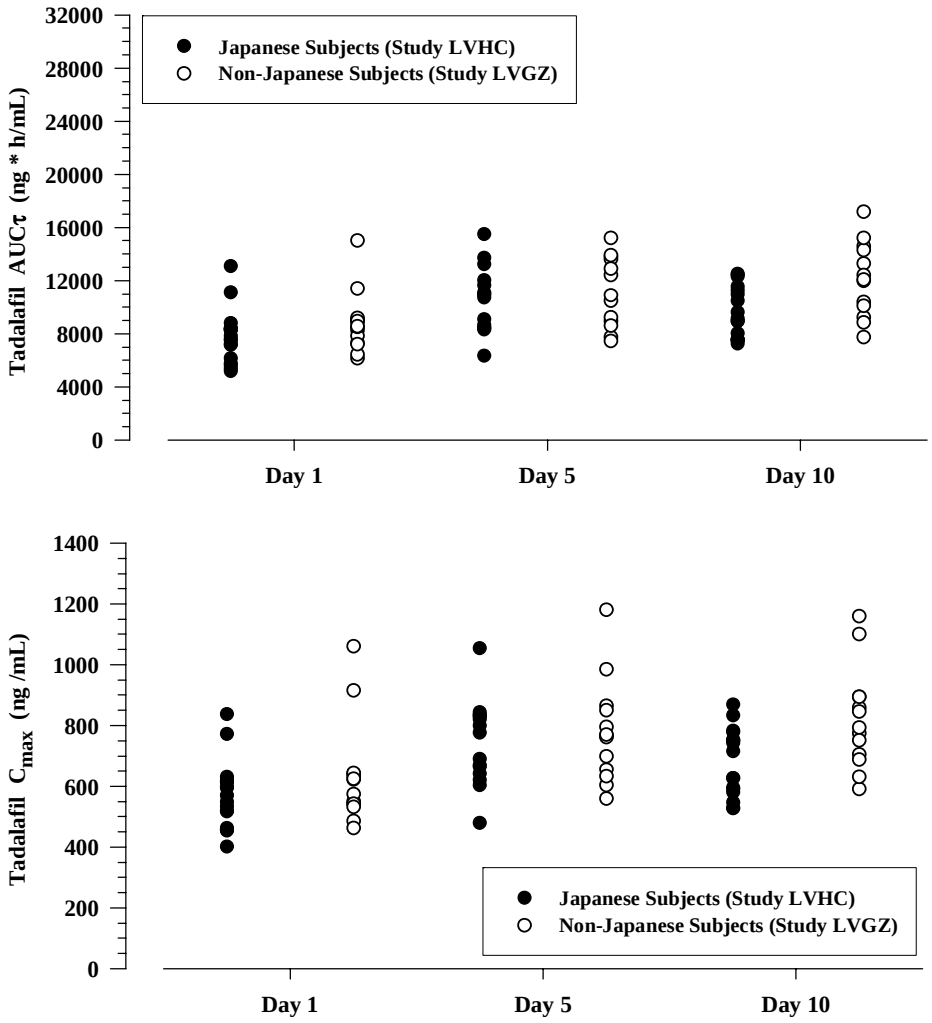
Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th to 95th percentiles.
Asterisks show data points outside this range. The number of observations is above each box.

Source: LVGY Population PK/PD Report, Figure LVGY.9.35

Figure 2.7.2.20. Individual tadalafil AUC_{ss} estimates versus tadalafil dose, stratified by Japanese and Caucasian ethnicity.

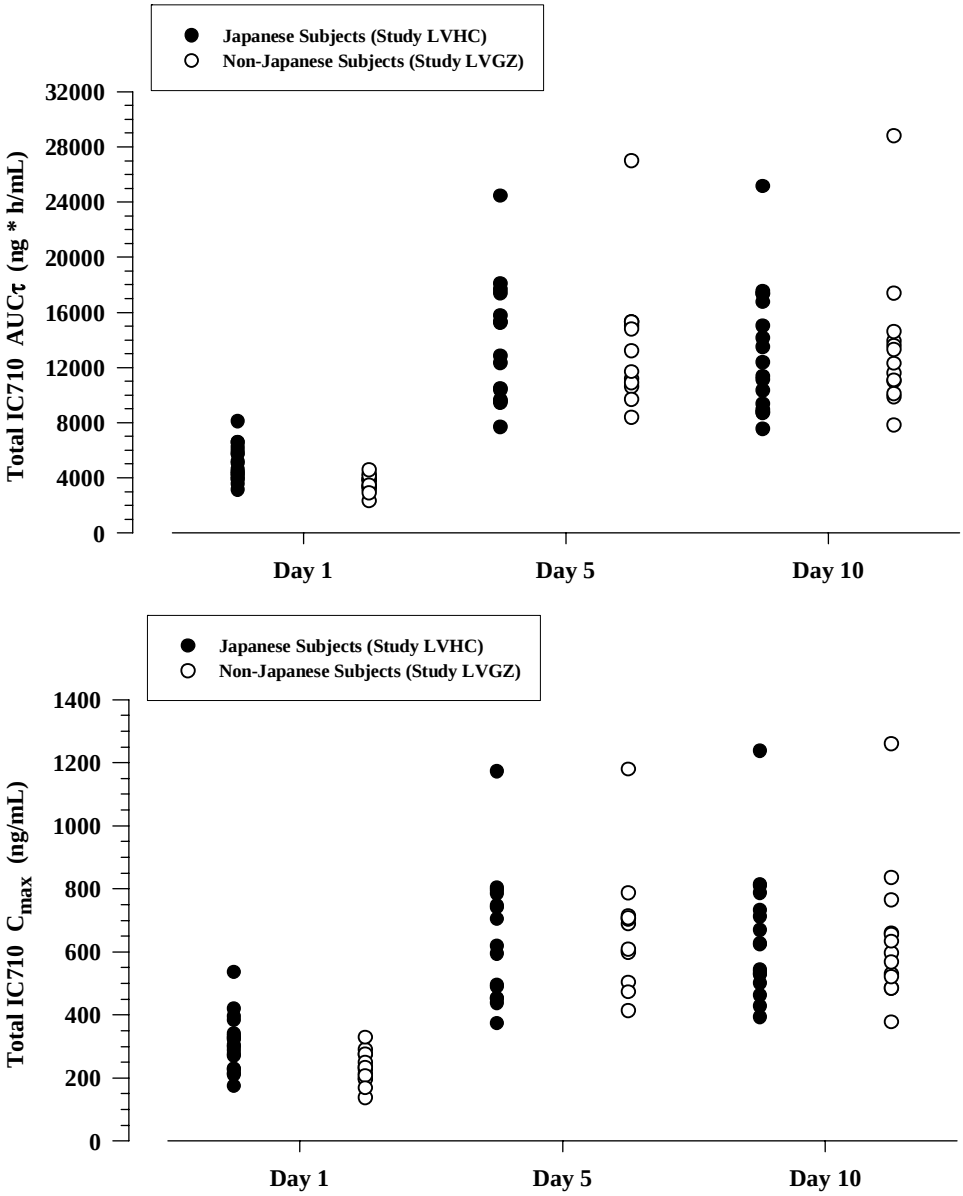
Additionally, to compare the tadalafil pharmacokinetics of Japanese and non-Japanese subjects following 40-mg once-daily multiple dose administration, results from

Study LVHC and those from Study LVGZ were evaluated. Notably, Study LVGZ included only non-Japanese male subjects (N=15; approximately 80% Caucasian) receiving once-daily multiple-dose 40-mg tadalafil; however, demographic and baseline characteristics of all subjects, irrespective of ethnicity, were generally similar. The pharmacokinetic parameters were examined by assessing the distribution of individual estimates of tadalafil (Figure 2.7.2.21) and total methylcatechol (Figure 2.7.2.22) AUC and C_{max}. Although there was a tendency for tadalafil systemic exposure to be lower in Japanese subjects, this difference was <25% irrespective of single- (Day 1) or multiple-dose (Day 10) administration and consistent with observation at lower doses of 20 mg (Study LVCS). The metabolic ratio following 40-mg tadalafil doses at steady-state (Day 10) was essentially similar in Japanese (1.24) and non-Japanese subjects (1.36), suggesting negligible differences in the biotransformation of tadalafil across ethnicity.



Source: CSR LVHC, Figure LVHC.7.10

Figure 2.7.2.21. Individual comparisons of tadalafil AUCτ (upper panel) and C_{max} (lower panel) in Japanese and non-Japanese subjects on Days 1, 5, and 10 following once-daily dose administration of 40-mg tadalafil.



Source: CSR LVHC, Figure LVHC.7.11

Figure 2.7.2.22. Individual comparisons of total methylcatechol metabolite AUCτ (upper panel) and C_{max} (lower panel) in Japanese and non-Japanese subjects on Days 1, 5, and 10 following once-daily dose administration of 40-mg tadalafil.

The results provided herein are consistent with historical data reported after single-dose administration of 5- to 40-mg tadalafil (Study LVCS, LVFU), at steady-state following once-daily 20-mg tadalafil (Study LVCT), and in subjects with ED (Studies LVDI/LVDJ); whereby no apparent pharmacokinetic differences necessitating dose adjustment was observed necessitating a dosing adjustment based upon ethnic origin.

2.7.2.3.2.3. Age

Pharmacostatistical comparisons of tadalafil in elderly and young subjects were assessed using both traditional, noncompartmental analyses of primary pharmacokinetic parameters from a single, small pharmacokinetic study (Study LVBW) in addition to population-based methods across clinical studies in subjects with ED and PAH.

As indicated in existing Cialis® labeling, no clinically important effect of age on tadalafil pharmacokinetics was observed following administration of a single 10-mg tadalafil dose to 12 elderly (65 to 78 years) male subjects, compared with the same number of young (19 to 45 years) male subjects (Study LVBW). Systemic exposure to tadalafil was higher in elderly subjects, the elderly/young ratio (90% CI) of LS means for AUC being 1.25 (0.97 to 1.61). Overall, 83% (10 of 12) of tadalafil exposures [AUC(0-∞)] in elderly subjects were within the maxima of that in young subjects; therefore, a high degree of concordance existed between the distribution of concentrations in elderly and young subjects and did not indicate a need for specific dose adjustments based upon age alone.

The elderly had a longer $t_{1/2}$ (21.6 hours versus 16.9 hours); therefore, greater accumulation might be expected for once-daily administration of 40 mg tadalafil. Plasma concentration-time profiles of tadalafil after a single dose were extrapolated to steady state during daily 40 mg dosing, by nonparametric superposition to predict the anticipated pharmacokinetic impact of chronic treatment. The simulated individual and mean concentrations in elderly subjects at steady-state are essentially similar to concentrations for the younger men, based upon Study LVBW (Figure 2.7.2.23). Although mean daily systemic exposure and C_{max} will be approximately 22% higher in elderly subjects than that in young subjects during daily 40 mg dosing, considerable overlap in the distribution of the data across age groups is apparent and does not support an overt, clinically relevant difference.

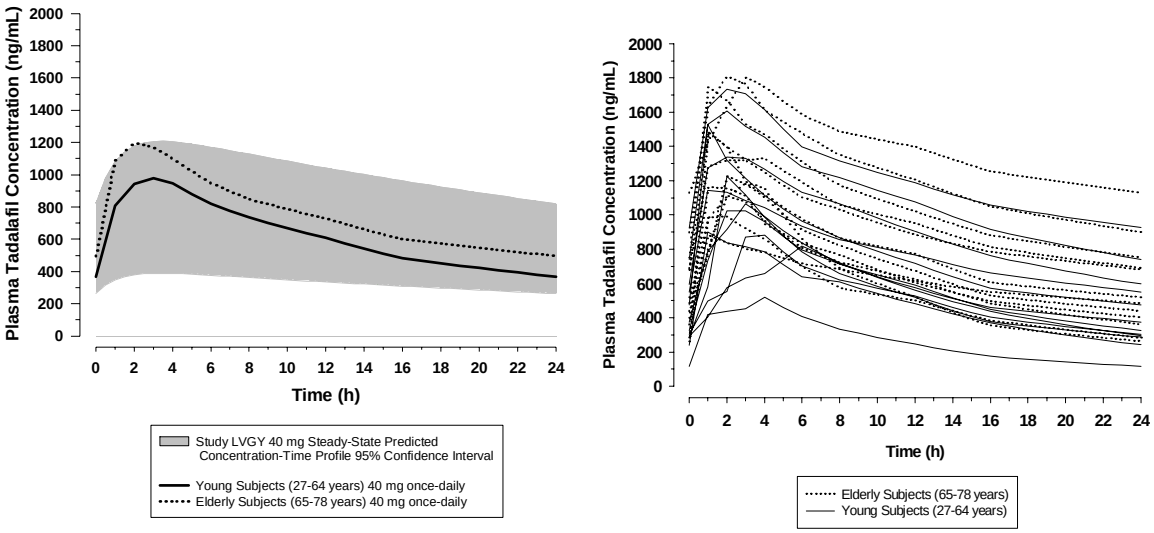


Figure 2.7.2.23. Simulated mean (left panel) and individual (right panel) tadalafil concentration-time profiles in young and elderly subjects following 40-mg daily administration.

The similarities in the distribution of Study LVBW data between elderly and young subjects likely elucidates the lack of any significant difference detected by the alternative, population-based approach (LVGY Population PK/PD Report). Data from a total of 222 subjects (72.8%) were <65 years and 83 subjects (27.2%) were ≥65 years were evaluable in the population pharmacokinetic analysis of subjects with PAH (Figure 2.7.2.24). Notably, the power of Study LVGY to detect a 20% difference in CL/F was >95%. Therefore, age would have likely been identified as a significant covariate if a clear pattern of increased (25%) elderly exposures were differentiable from young subjects.

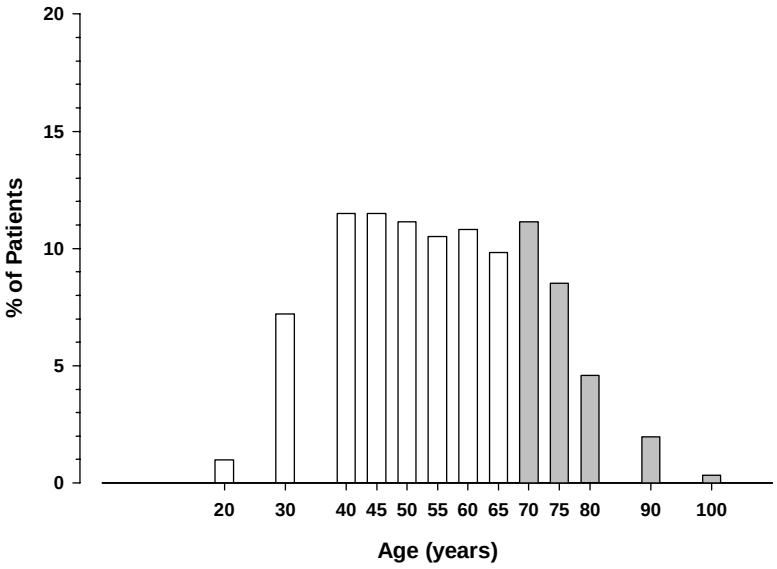


Figure 2.7.2.24. Distribution of age at entry for subjects with PAH in Study LVGY.

Further visual analyses according to age ranges generating mean ages mimicking those evaluated in Study LVBW for elderly (71 years) and young (36 years) subjects were conducted to explore discrete trends between exposure and age. The mean age at baseline of those subjects >65 years was 72 years of age and for those 128 (42.0%) subjects ≤50 years the mean age was 38.4 years and paralleled the demographic characteristics of individuals evaluated in Study LVBW. Following escalating doses of tadalafil in subjects with PAH; generally, modestly higher median exposures in elderly (≥65 years) compared with a younger cohort was discerned (Figure 2.7.2.25). The greatest magnitude of any mean difference was approximately 63.0% and observed following 10 mg daily tadalafil; otherwise, the distributions of exposures were largely overlapping with minimally higher (<20%) tadalafil exposures in elderly subjects relative to those less than 50 years of age following daily doses of 20 mg and 40 mg.

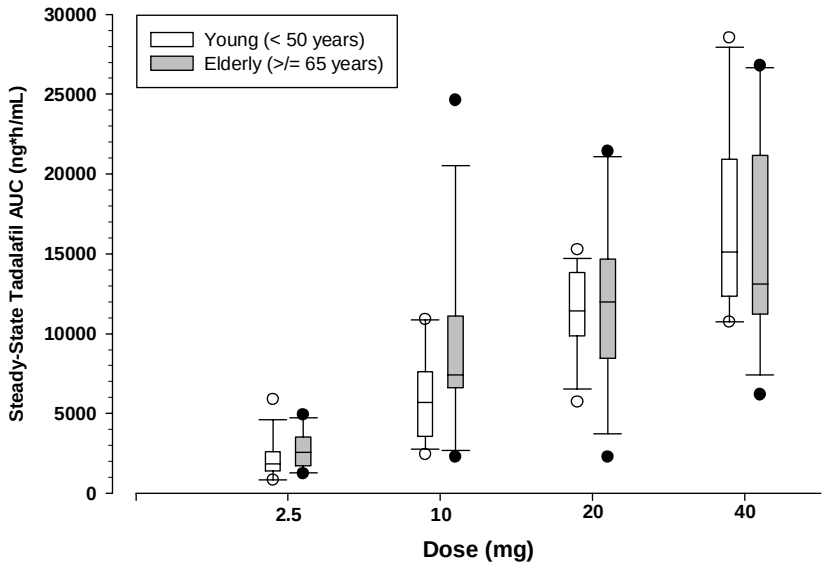


Figure 2.7.2.25. Predicted tadalafil exposure across subject age at entry for subjects in Study LVGY receiving tadalafil 2.5-, 10-, 20-, or 40-mg daily doses in the absence of concomitant bosentan use.

Given the collective pharmacokinetic data, noncompartmental (Study LVBW) and population-based analyses in ED (age range: 21 to 82 years) and PAH subjects (age range: 15 to 90 years) over 65 years of age, no dose adjustment in the elderly is warranted based upon pharmacokinetics alone. Further, as additional guidance is provided owing to greater sensitivity to medications, in general, in some older individuals, the proposed labeling is considered to be appropriate for tadalafil use in the elderly.

Additionally, in both the 16-week blinded portion of the Study LVGY, as well as open-label experience (Study LVGX) safety and tolerability of tadalafil appears similar between subjects 65 years or older and those under 65 years of age (Section 2.7.4).

2.7.2.3.2.4. Renal Impairment

Pharmacostatistical comparisons of tadalafil in subjects with varying degrees of renal impairment were assessed using both traditional, noncompartmental analyses of primary pharmacokinetic parameters from two pharmacokinetic studies (Studies LVAJ, LVDT) in addition to population-based methods across clinical studies in subjects with ED and PAH, based on the method of Cockcroft-Gault to estimate creatinine clearance and categorize renal impairment.

As summarized in existing Cialis® labeling, a single oral dose of tadalafil 5 mg or 10 mg was given to 12 healthy subjects (11 males and 1 female; 31 to 55 years old) and 8 subjects with mild and 8 subjects with moderate renal dysfunction (14 males and 2 females; 30 to 65 years old) to investigate the pharmacokinetics of tadalafil and total

methylcatechol metabolite (Study LVAJ). The pharmacokinetics of tadalafil and total methylcatechol metabolite following single oral dose administration of 5-, 10-, and 20-mg tadalafil, were determined in a total of 16 subjects with end-stage renal failure on hemodialysis (11 males and 5 females; 28 to 74 years old) (Study LVDT).

Following both 5- and 10-mg tadalafil, tadalafil exposure doubled in subjects with mild (creatinine clearance 51 to 80 mL/min) or moderate (creatinine clearance 31 to 50 mL/min) renal insufficiency. In subjects with end-stage renal disease on hemodialysis, there was a two-fold increase in C_{max} and 2.7- to 4.1-fold increase in AUC following single-dose administration of 10- or 20-mg tadalafil. Exposure to total methylcatechol was 2- to 4-fold higher in subjects with renal impairment, compared to those with normal renal function. Hemodialysis (performed between 24 and 30 hours postdose) contributed negligibly to tadalafil or metabolite elimination.

In the population pharmacokinetic analysis of subjects with PAH (Study LVGY), creatinine clearance, estimated using the Cockcroft-Gault method, was not identified as a covariate influencing tadalafil disposition (LVGY Population PK/PD Report). At study entry, 170 (55.7%) were categorized as having normal renal function compared to 90 (29.5%) and 39 (12.8%) subjects with mild and moderate renal impairment, respectively. Records from the 6 (1.97%) subjects determined to have severe impairment did not include dialysis status; therefore, classification with respect to end-stage renal disease with or without dialysis was not possible. Owing to the pathophysiology of PAH whereby, age, skeletal muscle dysfunction, and cachexia may potentially confound the interpretation of renal dysfunction such that abnormal creatinine clearance may not reflect chronic renal failure, the effect of renal impairment on tadalafil disposition and dosing recommendations related thereto are based upon the results from the clinical pharmacology studies (Studies LVAJ and LVDT) rather than the population analysis of Study LVGY.

Plasma concentration-time profiles of tadalafil after a single dose were extrapolated to steady-state for subjects with mild and moderate renal impairment and healthy subjects, by nonparametric superposition of Study LVAJ data to predict the anticipated pharmacokinetic impact of chronic treatment. The simulated mean concentration-time profiles in mild and moderate renal impairment following daily administration of 20 mg tadalafil at steady-state are generally similar to those for healthy subjects receiving 40 mg daily (Figure 2.7.2.26). In subjects with mild and moderate renal impairment receiving daily 20 mg tadalafil, steady-state tadalafil $AUC\tau$ is predicted to be approximately 10% higher and 3% lower, respectively, than that in subjects with normal renal function administered tadalafil 40 mg once-daily (Figure 2.7.2.27). The average tadalafil C_{max} following 20 mg daily is expected to be 20% and 14% higher in mild and moderate renal impairment, respectively, than that in healthy subjects given 40 mg (Figure 2.7.2.27). Additionally, with administration of daily 20-mg tadalafil, exposure to total methylcatechol metabolite was modestly (17% to 70%) higher in subjects with mild and moderate renal impairment, compared to those with normal renal function receiving

once-daily 40 mg, with overt overlap in the distribution across groups. Importantly, predicted mean plasma concentrations for subjects with mild to moderate renal insufficiency following 20 mg daily tadalafil largely remain within the 95% confidence interval of tadalafil 40 mg daily profiles estimated from subjects with PAH.

Although the safety and tolerability of tadalafil in subjects with PAH with renal insufficiency was similar to that in subjects with normal renal function, the number of subjects with mild or moderate renal impairment in Studies LVGY and LVGX was smaller than in the clinical trials in support of the ED indication (Section 2.7.4). Hence, based upon the comparable predicted pharmacokinetics between subjects with mild to moderate renal impairment receiving 20-mg tadalafil and those with normal renal function given 40 mg and the limited experience with doses exceeding 20 mg in subjects with renal insuffiency, once-daily 20-mg tadalafil is an appropriate starting dose for patients with mild and moderate renal impairment. In patients with severe renal insufficiency, tadalafil is not recommended due to increased tadalafil exposure, limited clinical experience, and the lack of ability to influence clearance by dialysis.

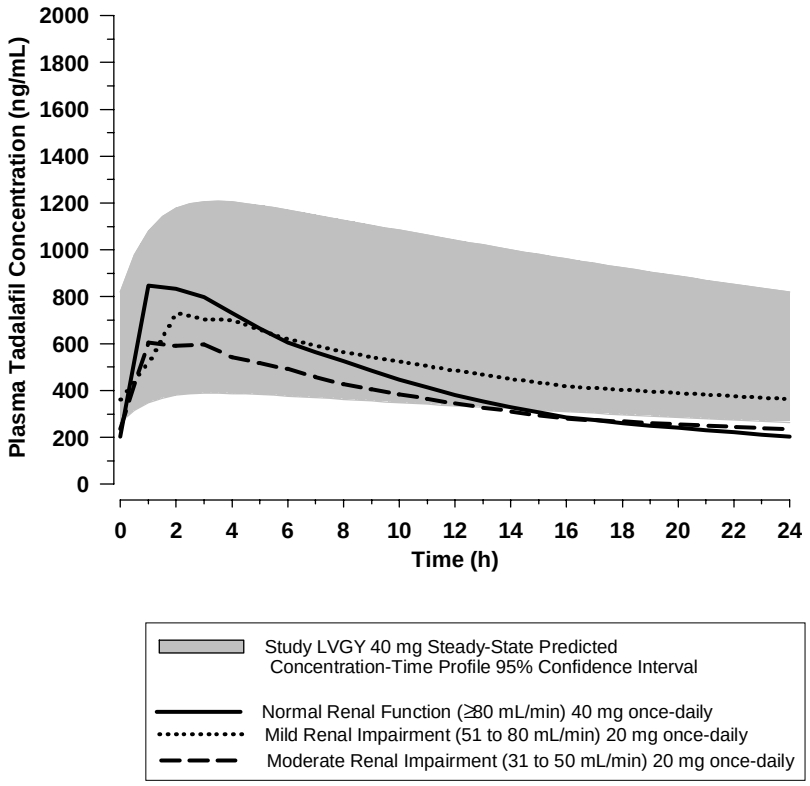


Figure 2.7.2.26. **Simulated mean tadalafil concentration-time profiles in healthy subjects after daily 40-mg tadalafil treatment and in subjects with mild or moderate renal impairment following 20-mg daily administration.**

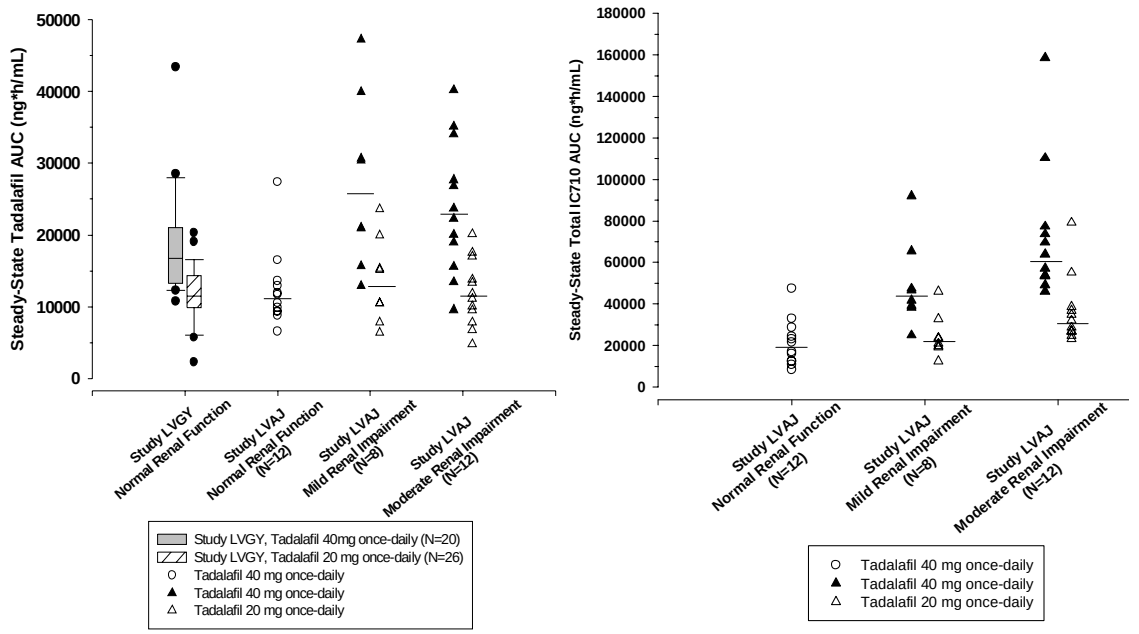


Figure 2.7.2.27. Predicted steady-state tadalafil (left panel) and total methylcatechol (right panel) exposure in subjects with normal renal function and mild or moderate renal impairment.

2.7.2.3.2.5. Hepatic Impairment

As provided in existing Cialis® labeling, a single oral dose of tadalafil 10 mg was given to 8 healthy adults and 25 subjects with hepatic dysfunction (16 males and 9 females; 25 to 63 years old) to investigate the effect of hepatic impairment on the pharmacokinetics of tadalafil (Study LVAK). Severity of hepatic dysfunction of subjects was classified according to Child-Pugh classification as mild (8 subjects; Class A, 5 to 6 points), moderate (8 subjects; Class B, 7 to 9 points), and severe (1 subject; Class C, 10 to 15 points), and very mild (8 subjects, with fatty liver less than 5 points).

Systemic exposure to tadalafil in subjects with very mild, mild, and moderate hepatic impairment is similar to that in age-matched healthy subjects receiving tadalafil 10 mg.

In the population pharmacokinetic analysis of subjects with PAH receiving once-daily tadalafil doses of 2.5, 10, 20, and 40 mg (LVGY Population PK/PD Report), Child-Pugh data were not collected and consequently could not be evaluated in the covariate analysis. Further, patients with evidence of clinically significant hepatobiliary disease based upon AST or ALT >3 times the upper limit of normal or severe hepatic impairment defined as Child-Pugh Class C were excluded from participation in Study LVGY and thus, no data are available from these patients. Moreover, at the initial visit, less than 4% of subjects with abnormal liver function tests (ALT or AST) were enrolled and only 7% of subjects were categorized as having elevated bilirubin with no subjects satisfying Hy's rule for hepatic impairment (ALT greater than 3 times the upper limit of normal and total

bilirubin greater than 2 times the upper limit of normal) (Bjornsson 2006). Thus, ALT, AST, and total bilirubin were omitted from the pharmacokinetic covariate analysis. Therefore, the noncompartmental analysis from Study LVAK provides the more robust assessment of the effects of hepatic dysfunction on tadalafil pharmacokinetics.

The comparable pharmacokinetics suggests administration of tadalafil 40 mg daily dosing to subjects with mild and moderate hepatic impairment may be reasonable; however, due to limited clinical experience with doses exceeding 10 mg in patients with chronic hepatic cirrhosis (Section 2.7.3) coupled with the potential of accumulation, a starting dose of tadalafil 20 mg once per day may be considered. The C_{max} and daily AUC [AUCτ] at steady-state following 20 mg daily dosing in mild and moderate hepatic impairment are expected to be approximately 1.77-fold higher relative to that following a 10 mg single dose. Analogous to that in Study LVAK, the steady-state tadalafil AUC and C_{max} in subjects with moderate hepatic impairment is predicted to be approximately 33% lower than that in subjects with mild hepatic dysfunction following tadalafil 20 mg daily dosing (Figure 2.7.2.28). However, despite moderate differences between mild and moderate hepatic impairment, predicted mean plasma concentration-time profiles and thereby systemic exposure remain with the 95% confidence interval of tadalafil 20 mg daily profiles estimated from subjects with PAH.

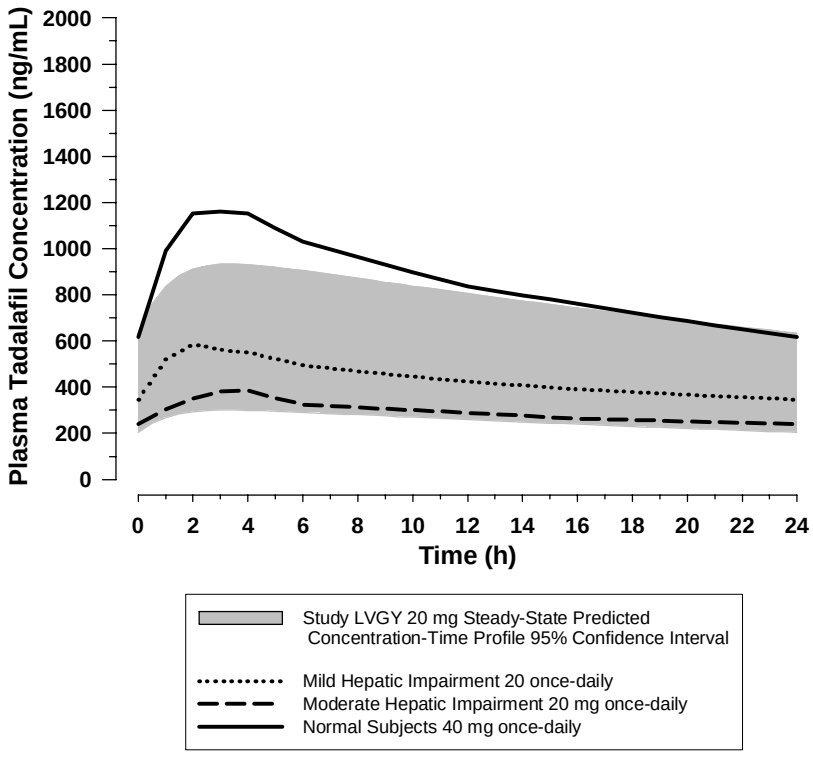


Figure 2.7.2.28. **Simulated mean tadalafil concentration-time profiles in healthy subjects after daily 40-mg tadalafil treatment and in subjects with mild or moderate hepatic impairment following 20-mg daily administration.**

Given that PK/PD modeling of the 6-minute walk observations from Study LVGY revealed that subjects who benefited most from tadalafil treatment received doses of at least 20-mg tadalafil once-daily, together with the comparable predicted plasma concentration-time profiles between subjects with mild and moderate hepatic impairment and subjects with PAH receiving daily doses of 20 mg tadalafil, suggests that tadalafil 20 mg once-daily is an appropriate starting dose and regimen for patients with chronic hepatic cirrhosis (Child-Pugh Class A and B). Tadalafil is not recommended for patients with PAH having severe hepatic impairment (Child-Pugh Class C), given insufficient clinical experience in this patient group.

2.7.2.3.3. Effect of Extrinsic Factors

In Study LVHM, once-daily administration of 40-mg tadalafil for 10 days resulted in a geometric mean C_{max} value of 827 µg/L and the highest individual plasma concentration was 1271 µg/L (3.26 µM). With a tadalafil concentration of 3.26 µM at the active site of the enzymes, the projected in vivo inhibition of metabolism mediated by CYPs 3A, 2C9, 1A2, and 2C19 would be 7.3%, 4.7%, 19.1%, and 4.3% respectively. Thus, in vitro studies predict that 40-mg tadalafil would not cause clinically significant inhibition of the metabolic clearance of drugs metabolized via these forms. However, tadalafil has been shown in vitro to inhibit CYP3A4 in a time- and concentration-dependent manner, indicative of mechanism-based inhibition (ADME 5) although this was not observed in subsequent clinical studies.

2.7.2.3.3.1. CYP3A4 Inhibition

Since tadalafil is primarily metabolized via CYP3A4, the effects of potent CYP3A4 inhibitors (ketoconazole and ritonavir) on the pharmacokinetics of tadalafil have been assessed. The effects of ketoconazole 400 mg once daily (Study LVEV) and ritonavir 500 mg or 600 mg twice daily (Study LVFV) on the pharmacokinetics of single-dose tadalafil 20 mg were investigated. Ketoconazole, a selective and potent inhibitor of CYP3A4, increased tadalafil AUC by 312% and C_{max} by 22% relative to values for tadalafil 20 mg alone and prolonged the mean half-life to 50.7 hours. Moreover, results of Study LVFV confirm the findings of Study LVEV that ketoconazole has a greater impact on tadalafil AUC than does ritonavir (200 mg, 500 mg or 600 mg twice daily).

Coadministration of 20-mg tadalafil once-daily with potent CYP3A4 inhibitors is expected to result in a daily systemic exposure that is 109% greater, and a C_{max} value 49% higher than corresponding values for daily 40 mg in the absence of potent CYP3A4 inhibitors (Figure 2.7.2.29). Whereas, only following coadministration of daily tadalafil 10 mg with ketoconazole would predicted tadalafil AUC and C_{max} be comparable to those following daily therapy with 40 mg tadalafil alone (Figure 2.7.2.29). As dose strengths other than 20 mg are not available for the treatment of PAH and given that PAH reflects a chronic disease requiring routine dosing to maximize compliance, tadalafil is not recommended in subjects with PAH taking potent inhibitors of CYP3A4.

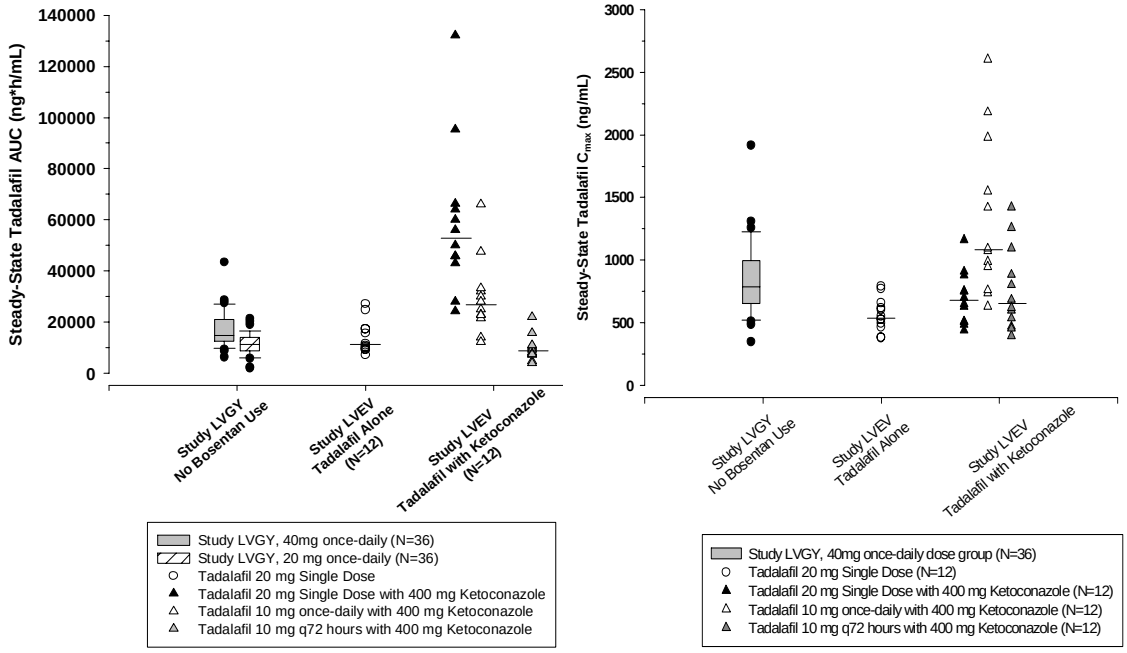


Figure 2.7.2.29. Predicted steady-state tadalafil exposure (left panel) and C_{max} (right panel) with and without concomitant ketoconazole administration.

2.7.2.3.3.2. CYP3A4 Induction

In the presence of rifampicin (Study LVAZ), a known potent inducer of CYP3A4, tadalafil concentrations were decreased. Geometric mean CL/F was increased approximately 8.5-fold with resulting clinically significant decreases in AUC (88% reduction) and C_{max} (46% reduction) when single-dose tadalafil (10 mg) was coadministered with rifampicin. Whereas, following coadministration with a moderate CYP3A4 inducer (bosentan), a reduction of only 41.5% and 26.6% in tadalafil AUC and C_{max}, respectively, was observed (Study LVGZ). It is unlikely that efficacy of tadalafil can be maintained with prolonged and greatly reduced tadalafil exposure. Therefore, given the magnitude of reduction in tadalafil with the coadministration of potent compared to moderate CYP3A4 inducers, chronic administration of potent inducers of CYP3A4 with tadalafil is not recommended.

Given that PK/PD modeling from Study LVGY indicated that doses of at least 20-mg tadalafil provided the greatest improvement in exercise capacity (Section 2.7.2.2.2.5) and as it is anticipated that concomitant administration of potent CYP3A4 inducers will reduce tadalafil exposures associated with 40-mg daily administration to those of a nominal dose of 5 mg or less (Figure 2.7.2.30), tadalafil is not recommended in those subjects chronically taking potent CYP3A4 inducers such as rifampicin. As concomitant administration of moderate or weak CYP3A4 inducers may be expected to decrease tadalafil exposures by less than 50% (Study LVGZ, LVGY Population PK/PD Report) such that once-daily 40 mg tadalafil exposures nominally become those of at least a

20-mg dose, no dose adjustment is recommended in those receiving concomitant treatment with moderate or weak CYP3A4 inducers.

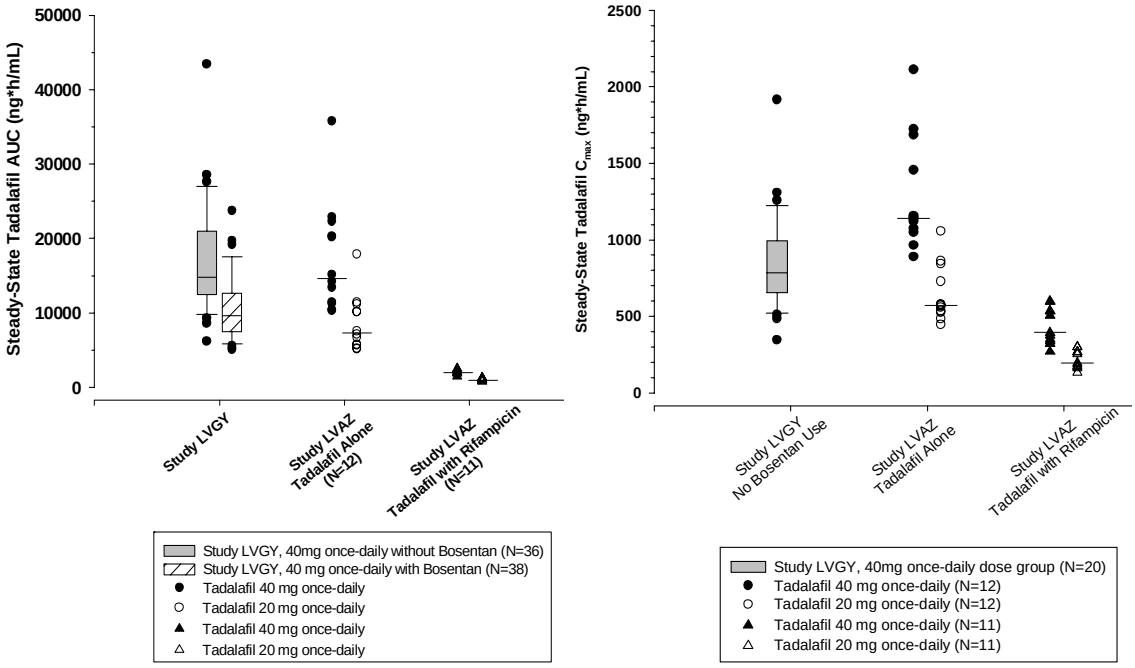


Figure 2.7.2.30. Predicted steady-state tadalafil exposure (left panel) and C_{max} (right panel) with and without concomitant rifampicin administration.

2.7.2.3.3.3. Pharmacodynamic Effects of Antihypertensive Agents

In the hypertensive patients and healthy subjects, no clinically significant pharmacodynamic interactions were observed during coadministration of tadalafil and various antihypertensive drugs. Therefore, coadministration of 10- or 20-mg tadalafil with these drugs is not believed to induce clinically significant effects of tadalafil on blood pressure or heart rate. The available data (Study LVDK) suggests that the effect on systemic blood pressure reaches a plateau at about 10 mg as the study determined that statistically 10 mg and 20 mg were similar with regard to vital sign changes. This would suggest that when 40 mg is administered to healthy subjects, the resulting decrease in blood pressure would be similar. However, based on the pharmacological action when coadministered, the hypotensive effects of antihypertensives may be potentiated because tadalafil has vasodilator properties. This effect appears to be more prominent in subjects whose blood pressure was not adequately controlled. Therefore, tadalafil should be administered with care when coadministered with antihypertensives.

2.7.2.3.3.4. Pharmacodynamic Effects of PAH Therapy Via Dual Endothelin Receptor Blockade

In Study LVGZ, healthy subjects received a total of 3 treatments: 40-mg tadalafil once daily for 10 days, 125-mg bosentan twice daily for 10 days, and the combination of tadalafil and bosentan for 10 days. Mean supine and standing blood pressure generally decreased from baseline up to 12 hours postdose for all treatments on Study Days 1 and 10. The decreases were generally similar when tadalafil was administered alone and with bosentan although decreases in supine systolic blood pressure on both days and standing diastolic blood pressure on Study Day 10 were greater when tadalafil was administered with bosentan. A small number of subjects had potentially clinically significant decreases in standing and supine systolic blood pressure and standing diastolic blood pressure, based upon prespecified criteria. However, 36% to 64% of subjects on each treatment had a supine diastolic blood pressure of <45 mm Hg on at least one occasion.

2.7.2.4. Special Studies

Special studies are not applicable for this application. Historical data for this category are summarized previously (Section 2.7.2.1.1.2).