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2.7.2.5. Appendix

Table 2.7.2.5.1. Table of In Vitro Studies Using Human Biomaterials

ADME Report No.	Objectives	Method	Drug	Biomaterials	Result (arithmetic mean)
25	In vitro protein binding	In vitro equilibrium dialysis	^{14}C-tadalafil 10-10000 ng/mL	Human plasma	The binding of ^{14}C-tadalafil was about 94 ± 2% (SD).
26	In vitro protein binding	In vitro equilibrium dialysis	^{14}C-tadalafil 12-1200 ng/mL	Human plasma protein	^{14}C-tadalafil was 85% bound to albumin, 90% bound to alpha1-glycoprotein and 15% gannma globlins and 96% bound to protein mix.
24	In vitro whole blood distribution	In vitro	^{14}C-tadalafil 40-10000 ng/mL	Human whole blood	Plasma to whole blood concentration ratio: 1.39.
7	In vitro metabolism	In vitro	^{14}C-tadalafil 100 µM	Human liver slice	Metabolites: methylcatechol glucronide, N-desmethyl and three monohydroxylated metabolites.
8	In vitro metabolism	In vitro	^{14}C-tadalafil 10µM	Human liver microsomes	Metabolites: Catechol.
34	In vitro metabolism	In vitro	Tadalafil 1.8 µM	Human liver microsomes CYP enzyme expressed microsomes	Expressed CYP3A4 was able to form IC711 at a rate that was at least13-fold greater than the rates obtained with CYP2C8, CYP2C9, CYP2C19, and CYP2D6. Monoclonal antibodies to CYP3A4 inhibited the formation of IC711 by at least 84%. In contrast, antibodies to the CYP2C subfamily of enzymes and to CYP2D6 inhibited the reaction by less than 13%.

(continued)

Table 2.7.2.5.1. Table of In Vitro Studies Using Human Biomaterials (Concluded)

ADME Report No.	Objectives	Method	Drug	Biomaterials	Result (arithmetic mean)
4	In vitro interaction	In vitro	Midazolam 5, 10, 25, 50, 100 μM (tadalafil: 1, 10, 25, or 50 μM) Diclofenac (2.5, 5.0, 10, 25, 50 μM (tadalafil: 10, 25, 50, 100 μM) Phenacetin 12.5, 25, 50, 75, 100 μM (tadalafil: 0.1, 1.0, 10, 25 μM)	Human liver microsomes	Apparent Ki CYP3A Midazolam: 41.2 ± 4.5 μM CYP2C9: Diclofenac 65.8 ± 6.1 μM CYP1A2: Phenacetin 13.8 ± 0.5 μM (SE)
89	In vitro interaction	In vitro	Tadalafil: 35, 50, 65, 80 μM S-mephenytoin: 5.0, 10, 25, 50, 100 μM	Human liver microsomes	Apparent Ki = 72.7 ± 8.4 μM (SE)
5	In vitro enzyme inhibition	In vitro	Tadalafil 25 μM	Human liver microsomes	The maximum inhibition observed was 76% following a 60-minute preincubation of human liver microsomes with 25 μM (9.7 μg/mL) tadalafil and NADPH.
43	In vitro enzyme induction/inhibition	In vitro	Tadalafil (0.1-50 μM)	Human primary cultures of hepatocytes	Primary cultures of human hepatocytes were treated for 48 hours with tadalafil at concentrations ranging from 0.1 to 50 μM. Tadalafil did not exhibit a consistent effect on CYP1A2. Tadalafil appeared to produce both mechanism-based inhibition of CYP3A activity and induction of CYP3A protein expression.

Abbreviations: CYP = cytochrome P450; Ki = inhibition constant; NADPH = reduced form of nicotinamide-adenine dinucleotide phosphate; No. = number; SD = standard deviation; SE = standard error.

Table 2.7.2.5.2. Index of In Vitro Studies Using Human Biomaterials that Support Clinical Development

Study ID	Study Title
Protein Binding	
BPW507	The Binding of 14C-GF196960 in Rat, Dog and Human Plasma Proteins In Vitro
BPW770	The Binding of 14C-GF196960 to Individual Human Plasma Protein In Vitro
Whole Blood Distribution	
BPW495	The Distribution of 14C-GF196960 in Rat, Dog and Human Whole Blood In Vitro
Metabolite Identification and Formation	
ADME 7	In Vitro Metabolism of tadalafil (LY450190) in Human, Rat, Mouse, and Dog Liver Slices
ADME 8	In Vitro Metabolism of tadalafil (LY450190) by Microsomes from the Livers of Rat, Dog, Mouse, and Human
1999IV-EI004	Identification of the Human Enzyme Responsible for the Formation of the Catechol Metabolite (IC711) of tadalafil (LY450190)
Drug Interaction Assessments	
ADME 4	In Vitro Interaction of tadalafil (LY450190) with Human Cytochromes P450 CYP3A, CYP2D6, CYP2C9, and CYP1A2
2001IV-DI005	In Vitro Interaction of tadalafil with Human Cytochrome P450 2C19
ADME 5	Examination of Mechanism-Based Inhibition of Cytochrome P450 CYP3A by tadalafil (LY450190)
ADME 43	Examination of CYP1A2 and CYP3A Induction/Inhibition by IC351 (LY450190) in Primary Cultures of Human Hepatocytes

Abbreviation: CYP = cytochrome P450.

Table 2.7.2.5.3. Summary of Pharmacokinetics in Results from Studies Conducted in Support of PAH Indication

Protocol Alias	Study Objectives	Study design	Treatment (Dose, Dosage formulation)	No. of Subjects for PK analysis	Geometric Mean (%CV) of PK parameter						Ratio of geometric least squares means (90%CI)	
					C_{max} (µg/L)	t_{max}[a] (h)	AUC (µg*hr /L)	$t_{1/2}$ (h)	CL/F (L/h)	Vz/F (L)	C_{max}	$AUC_{(0-\tau)}$
LVGZ	PK interaction of tadalafil and bosentan	Open-label, randomized, 3-period crossover	Tadalafil, QD, 10 Days 2 x 20 mg	13 HV males	807 (19.8)	4.00	11800[b] (23.9)	15.8 (23.3)	3.39 (23.9)	77.1 (20.8)		
			Bosentan BID, 10 Days 125 mg	14 HV males	1190 (44.2)	4.02	4700[c] (37.2)		26.6 (37.2)			
			Tadalafil 2 x 20 mg + Bosentan BID 125 mg, both for 10 days	14 HV males	Tadalafil PK Information							
					598 (20.2)	3.00	6950[b] (23.8)	12.0 (23.1)	5.76 (23.8)	54.4 (22.5)	Tadalafil + bosentan / tadalafil	
											0.734 (0.680, 0.793)	0.585[b] (0.553, 0.620)
					Bosentan PK Information							
					1420 (43.5)	3.00	5330[c] (37.7)		23.4 (37.7)[z]		Tadalafil + bosentan / bosentan	
											1.195 (1.054, 1.356)	1.126[c] (1.020, 1.243)
LVHC	Safety, and PK in Japanese Subjects	Double-blind, randomized, placebo controlled	10 days QD PO tadalafil (2 x 20 mg) or placebo	15 HV (Japanese)	688 (16.1)		9630[b] (20.5)	14.3 (12.1)	4.15 (20.5)	85.7 (19.5)		

(continued)

Table 2.7.2.5.3. Summary of Pharmacokinetics in Results from Studies Conducted in Support of PAH Indication (Continued)

Protocol Alias	Study Objectives	Study design	Treatment (Dose, Dosage formulation)	No. of Subjects for PK analysis	Geometric Mean (%CV) of PK parameter						Ratio of geometric least squares means (90%CI)	
					C_{max} (µg/L)	t_{max}[a] (h)	AUC (µg*hr /L)	$t_{1/2}$ (h)	CL/F (L/h)	Vz/F (L)	C_{max}	$AUC_{(0-\tau)}$
LVHL	Effect of multiple tadalafil doses on digoxin PK, and safety	Open-label, single sequence	Digoxin 0.50 mg BID Day 1, Digoxin 0.25 mg QD, Day 2-17 + Placebo	20 HV	1.48 (26.1)	1.30	16.5[b] (23.8)		15.1 (23.8)			
			Tadalafil 2x20 mg QD + Digoxin 0.25 mg QD x final 10 days of digoxin treatment	19 HV	1.40 (20.4)	1.50	15.1[b] (20.3)		16.6 (20.3)		Digoxin + tadalafil / digoxin	
											0.949 (0.863, 1.04)	0.905[b] (0.856, 0.957)

(continued)

Table 2.7.2.5.3. Summary of Pharmacokinetics in Results from Studies Conducted in Support of PAH Indication (Continued)

Protocol Alias	Study Objectives	Study design	Treatment (Dose, Dosage formulation)	No. of Subjects for PK analysis	Geometric Mean (%CV) of PK parameter						Ratio of geometric least squares means (90%CI)	
					C_{max} (µg/L)	t_{max}[a] (h)	AUC (µg*hr /L)	$t_{1/2}$ (h)	CL/F (L/h)	Vz/F (L)	C_{max}	$AUC_{(0-\tau)}$
LVHM	PK of a combination oral contraceptive and safety with and without tadalafil	Double-blind, 3-period, 2-sequence, randomized, crossover, Placebo control	Tadalafil PK Information									
			Tadalafil 2x20 mg QD, 21 days + oral contraceptive (30 µg ethinylestradiol and 150 µg levonorgestrel) QD, 21 days	28 HV	827 (19.6)	4.00	12521[b] (23.0)		3.19 (23.0)			
			Ethinylestradiol PK Information									
			Placebo QD, 21 days + oral contraceptive (30 µg ethinylestradiol and 150 µg levonorgestrel) QD, 21 days	26 HV	65.9 (36.0) pg/mL	3.0	739[b] (33.5) pg*h/mL					

(continued)

Table 2.7.2.5.3. Summary of Pharmacokinetics in Results from Studies Conducted in Support of PAH Indication (Continued)

Protocol Alias	Study Objectives	Study design	Treatment (Dose, Dosage formulation)	No. of Subjects for PK analysis	Geometric Mean (%CV) of PK parameter						Ratio of geometric least squares means (90%CI)	
					C_{max} (µg/L)	t_{max}[a] (h)	AUC (µg*hr /L)	$t_{1/2}$ (h)	CL/F (L/h)	Vz/F (L)	C_{max}	$AUC_{(0-\tau)}$
			Ethinylestradiol PK Information (continued)									
LVHM	PK of a combination oral contraceptive and safety with and without tadalafil	Double-blind, 3-period, 2-sequence, randomized, crossover, Placebo control	Tadalafil 2x20 mg QD, 21 days + oral contraceptive (30 µg ethinylestradiol and 150 µg levonorgestrel)	28 HV	11.5 (33.0) pg/mL	2.58	971[b] (33.4) pg*h/mL				Oral contraceptive + tadalafil/ oral contraceptive	
											1.70 (1.58, 1.82) pg/mL	1.26[b] (1.18, 1.34) pg*h/mL
			Levonorgestrel PK Information									
			Placebo, QD + oral contraceptive (30 µg ethinylestradiol and 150 µg levonorgestrel) QD, 21 days	26 HV	6047 (35.1) pg/mL	2.0	77890[b] (49.2) pg*h/mL					

(continued)

Table 2.7.2.5.3. Summary of Pharmacokinetics in Results from Studies Conducted in Support of PAH Indication (Concluded)

Protocol Alias	Study Objectives	Study design	Treatment (Dose, Dosage formulation)	No. of Subjects for PK analysis	Geometric Mean (%CV) of PK parameter						Ratio of geometric least squares means (90%CI)	
					C_{max} (µg/L)	t_{max}[a] (h)	AUC (µg*hr /L)	$t_{1/2}$ (h)	CL/F (L/h)	Vz/F (L)	C_{max}	$AUC_{(0-\tau)}$,
			Levonorgestrel PK Information (continued)									
LVHM	PK of a combination oral contracep-tive and safety with and without tadalafil	Double-blind, 3-period, 2-sequence, randomized, crossover, Placebo control	Tadalafil 2x20 mg QD, 21 days + oral contraceptive (30 µg ethinylestradiol and 150 µg levonorgestrel) QD, 21 days	28 HV	6245 (33.7) pg/mL	1.54	80479[b] (43.2) pg*h/mL				Oral contraceptive + tadalafil/ oral contraceptive	
											1.02 (0.969, 1.08) pg/mL	1.02[b] (0.961, 1.08) pg*h/mL

Abbreviations: AUC = area under the concentration time curve from time 0 to infinity unless otherwise indicated.; BID = twice daily; C_{max} = maximal concentration; CI = confidence interval; CL/F = apparent clearance; CV = coefficient of variation; h = hours; HV = healthy volunteers; No. = number; PK = pharmacokinetics; PO = orally; QD = once daily; $t_{1/2}$ = terminal half-life; t_{max} = time to maximal concentration; Vz/F = apparent volume of distribution.

[a] Median

[b] $AUC_{(0-24)}$, at steady state

[c] $AUC_{(0-12)}$ at steady state

Note: µg/L is equivalent to ng/mL.

Table 2.7.2.5.4. Summary of Pharmacokinetics in Healthy Volunteers in Historic Studies

Protocol Alias	Study Objectives	Study design	Treatment (Dose, Dosage formulation)	No. of Subjects for PK analysis	Geometric Mean (%CV) of PK parameter						Ratio of geometric least squares means (90%CI)	
					C_{max} (µg/L)	t_{max}[a] (h)	AUC (µg*hr /L)	$t_{1/2}$ (h)	CL/F (L/h)	Vz/F (L)	C_{max}	AUC(0-∞)
LVCS	Safety in Japanese and Western origin and the comparison of PK following single tadalafil	Double-blind, placebo controlled, randomized, 2-site crossover	Tadalafil 1 x 5 mg	Japanese N=23	95.6 (30.0)	3.00	1784 (35.3)	14.2 (19.9)	2.80 (35.3)	57.2 (31.1)	Japanese/Western origin	
				Western origin N=24	101 (31.4)	2.04	1928 (36.5)	15.7 (35.1)	2.59 (36.5)	58.6 (27.0)	0.95 (0.82,1.10)	0.92 (0.78,1.10)
			Tadalafil 1 x 10 mg	Japanese N=23	174 (26.5)	3.00	3319 (32.5)	14.6 (20.9)	3.01 (32.5)	63.5 (24.8)	Japanese/Western origin	
				Western origin N=24	187 (29.0)	2.00	3701 (39.3)	15.4 (32.2)	2.70 (39.3)	60.1 (31.4)	0.93 (0.81,1.06)	0.90 (0.76,1.06)
			Tadalafil 1 x 20 mg	Japanese N=24	292 (26.1)	3.00	5825 (23.2)	13.6 (17.1)	3.43 (23.2)	67.3 (16.4)	Japanese/Western origin	
				Western origin N=24	318 (29.9)	3.00	7175 (40.3)	15.7 (30.1)	2.79 (40.3)	63.3 (26.6)	0.92 (0.81,1.05)	0.81 (0.70,0.95)
			Tadalafil 2 x 20 mg	Japanese N=23	562 (26.6)	3.00	10371 (32.3)	14.9 (20.0)	3.86 (32.3)	83.1 (20.8)	Japanese/Western origin	
				Western origin N=22	446 (20.2)	3.00	14015 (26.3)	16.5 (26.9)	2.85 (26.3)	67.8 (24.3)	0.79 (0.71,0.89)	0.74 (0.64,0.86)

(continued)

Table 2.7.2.5.4. Summary of Pharmacokinetics in Healthy Volunteers (Continued)

Protocol Alias	Study Objectives	Study design	Treatment (Dose, Dosage formulation)	No. of Subjects for PK analysis	Geometric Mean (%CV) of PK parameter						Ratio of geometric least squares means (90%CI)	
					C_{max} (µg/L)	t_{max}[a] (h)	AUC (µg*hr /L)	$t_{1/2}$ (h)	CL/F (L/h)	Vz/F (L)	C_{max}	AUC(0-∞)
LVCT	Safety and PK of tadalafil multiple – dose in Japanese males	Double-blind, placebo controlled	Tadalafil 20 mg QD, 10 Days	17 HV	461 (18.4)	3.00	6430 (18.7)	14.5 (17.9)	3.11 (18.7)	64.9 (18.0)	-	-
LVDK	Cardio-vascular effect and PK in tadalafil multiple dose	Double-blind, randomized, parallel	Part A (cardio-vascular) tadalafil 1 x 10 mg, 2 x 10 mg	-	-	-	-	-	-	-	-	-
			Part B (PK comparison) tadalafil 1 x 10 mg	15 HV	286 (25.7)	2.00	3887 (29.5)	18.0 (28.0)	2.57 (29.5)	67.0 (23.1)	-	-
			Part B (PK comparison) tadalafil 2 x 10 mg	13 HV	481 (31.0)	2.00	7389 (38.2)	18.7 (40.4)	2.71 (38.2)	73.1 (22.9)	-	-

(continued)

Table 2.7.2.5.4. Summary of Pharmacokinetics in Healthy Volunteers in Historic Studies (Concluded)

Protocol Alias	Study Objectives	Study design	Treatment (Dose, Dosage formulation)	No. of Subjects for PK analysis	Geometric Mean (%CV) of PK parameter						Ratio of geometric least squares means (90%CI)	
					C_{max} (µg/L)	t_{max}[a] (h)	AUC (µg*hr /L)	$t_{1/2}$ (h)	CL/F (L/h)	Vz/F (L)	C_{max}	AUC(0-∞)
LVAA	^{14}C-tadalafil Metabolism and distribution	Open-label	^{14}C-tadalafil (oral solution) 100 mg	6 HV	727 (37.1)	4.00	23684 (25.7)	15.3 (28.8)	4.22 (25.7)	93.3 (25.8)	-	-
LVAD	Safety, tolerability, and PK	Open-label,	Part 1: Single dose tadalafil 10 mg	12 HV female	140 (21.0)	3.51	4097 (28.2)	19.8 (26.1)	2.44 (28.2)	69.8 (19.3)	female (Day 1) / male (Day 1)	
				12 HV male	142 (26.5)	3.50	3565 (23.1)	16.6 (21.0)	2.81 (23.1)	67.2 (16.5)		1.15 (0.96, 1.37)
			Part 2: 10 mg tadalafil, QD, PO, x 10 days	12 HV female	277 (26.0)	3.02	4184 (33.1)	20.3 (25.5)	2.39 (33.1)	69.9 (25.4)		
				12 HV male	232 (26.6)	4.00	3633 (29.5)	17.8 (27.4)	2.75 (29.5)	70.6 (17.1)		

Abbreviations: AUC = area under the concentration time curve from time 0 to infinity unless otherwise indicated.; C_{max} = maximal concentration; CI = confidence interval; CL/F = apparent clearance; CV = coefficient of variation; h = hours; HV = healthy volunteers; No. = number; PK = pharmacokinetics; PO = orally; QD = once daily; $t_{1/2}$ = terminal half-life; t_{max} = time to maximal concentration; Vz/F = apparent volume of distribution.

[a] Median

Note: µg/L is equivalent to ng/mL.

Table 2.7.2.5.5. Summary of Pharmacokinetics in Special Populations in Historic Studies

Protocol Alias	Study Objectives	Study design	Treatment (Dose, Dosage formulation)	No. of Subjects for PK analysis	Geometric Mean (%CV) of PK parameter						Ratio of geometric least squares means (90%CI)	
					C_{max} (µg/L)	t_{max}[a] (h)	AUC (µg*hr /L)	$t_{1/2}$ (h)	CL/F (L/h)	Vz/F (L)	C_{max}	AUC(0-∞)
LVAJ	Comparison of PK, safety, tolerability in the patients with mild or moderate renal impairment and HV	Open-label, parallel	Tadalafil 5 mg	4 HV	101 (31.2)	1.00	1472 (25.1)	18 (18.3)	3.40 (25.1)	87.1 (11.3)	-	
				3 mild renal impairment	111 (17.4)	2.00	3119 (62.3)	25 (66.9)	1.60 (62.3)	57.6 (22.0)		
				6 moderate renal impairment	136 (13.2)	0.500	3135 (37.5)	26 (41.7)	1.59 (37.5)	59.9 (25.3)		
			Tadalafil 10 mg	8 HV	183 (31.2)	1.00	2868 (44.2)	14 (45.8)	3.49 (44.2)	71.8 (39.5)		
				5 mild renal impairment	217 (21.0)	2.00	6280 (46.1)	26 (32.7)	1.59 (46.1)	59.2 (15.8)		
				6 moderate renal impairment	220 (22.2)	2.00	4911 (50.1)	22 (43.0)	2.04 (50.1)	65.9 (17.5)		

(continued)

Table 2.7.2.5.5. Summary of Pharmacokinetics in Special Populations in Historic Studies (Continued)

Protocol Alias	Study Objectives	Study design	Treatment (Dose, Dosage formulation)	No. of Subjects for PK analysis	Geometric Mean (%CV) of PK parameter						Ratio of geometric least squares means (90%CI)	
					C_{max} (µg/L)	t_{max}[a] (h)	AUC (µg*hr /L)	$t_{1/2}$ (h)	CL/F (L/h)	Vz/F (L)	C_{max}	AUC(0-∞)
LVBW	PK comparison in elderly and young following tadalafil single dose	Open-label, parallel	Tadalafil 10 mg	12 elderly male	196 (26.9)	2.00	4881 (31.7)	21.6 (39.0)	2.05 (31.7)	63.9 (25.5)	elderly/young	
				12 young male	183 (25.5)	2.50	3896 (42.6)	16.9 (29.1)	2.57 (42.6)	62.5 (17.3)	1.07 (0.895,1.28)	1.25 (0.972,1.61)
LVDT	Tolerability and PK in the patients with end-stage renal failure who were receiving haemodialysis	Open-label	Tadalafil 5 mg	6 ESRF Poland	78.6 (21.6)	3.00	1633 (63.0)	13.8 (51.3)	3.06 (63.0)	60.9 (18.2)		
			Tadalafil 10 mg	6 ESRF Poland	186 (17.2)	4.00	4023 (38.2)	15.2 (41.6)	2.49 (38.2)	55.0 (19.9)		
				6 ESRF UK	394 (20.8)	2.04	13749 (36.7)	24.8 (37.9)	0.73 (36.7)	26.1 (22.9)		
			Tadalafil 20mg	6 ESRF UK	621 (26.6)	2.04	18090 (38.8)	18.7 (34.6)	1.11 (38.8)	29.8 (16.9)		

(continued)

Table 2.7.2.5.5. Summary of Pharmacokinetics in Special Populations in Historic Studies (Concluded)

Protocol Alias	Study Objectives	Study design	Treatment (Dose, Dosage formulation)	No. of Subjects for PK analysis	Geometric Mean (%CV) of PK parameter						Ratio of geometric least squares means (90%CI)	
					C_{max} (µg/L)	t_{max}[a] (h)	AUC (µg*hr /L)	$t_{1/2}$ (h)	CL/F (L/h)	Vz/F (L)	C_{max}	AUC(0-∞)
LVAK	Comparison of PK, safety, tolerability in patients with very mild, mild, moderate, and severe hepatic impairment and HV	Open-label, parallel	Tadalafil 10 mg	8 HV	180 (38.1)	2.50	5823 (74.4)	24.2 (52.6)	1.72 (74.4)	59.9 (30.0)	-	
			Tadalafil 10 mg	8 very mild hepatic impairment	133 (20.8)	3.01	3961 (34.3)	24.7 (42.6)	2.52 (34.3)	90.1 (19.3)	very mild/HV	
											0.74 (0.57,0.96)	0.68 (0.44,1.05)
			Tadalafil 10 mg	8 mild hepatic impairment	146 (22.8)	2.00	5760 (51.7)	34.9 (48.4)	1.74 (51.7)	87.5 (24.9)	mild/HV	
											0.81 (0.63,1.05)	0.99 (0.64,1.53)
			Tadalafil 10 mg	8 moderate hepatic impairment	101 (39.4)	2.50	4049 (55.5)	37.8 (62.0)	2.47 (55.5)	135 (55.0)	moderate/HV	
											0.56 (0.43,0.73)	0.70 (0.45,1.08)
LVAS	Comparison of PK, safety, tolerability in the patients with diabetes and HV	Open label parallel	Tadalafil 10 mg	12 diabetes	184 (27.1)	3.00	3458 (38.2)	13.8 (33.2)	2.89 (38.2)	57.4 (18.2)	diabetes/HV	
											0.95 (0.79,1.13)	0.81 (0.63,1.06)
				12 HV	193 (21.6)	2.00	4249 (36.2)	17.1 (26.8)	2.35 (36.2)	58.2 (23.3)	-	

Abbreviations: AUC = area under the concentration time curve from time 0 to infinity unless otherwise indicated.; C_{max} = maximal concentration; CI = confidence interval; CL/F = apparent clearance; CV = coefficient of variation; h = hours; HV = healthy volunteers; No. = number; PK = pharmacokinetics; $t_{1/2}$ = terminal half-life; t_{max} = time to maximal concentration; Vz/F = apparent volume of distribution.

[a] Median.

Note: µg/L is equivalent to ng/mL.

Table 2.7.2.5.6. Summary of Pharmacokinetic Interaction Studies in Historic Studies

Protocol Alias	Study Objectives	Study design	Treatment (Dose, Dosage formulation)	No. of Subjects for PK analysis	Geometric Mean (%CV) of PK parameter						Ratio of geometric least squares means (90%CI)	
					C_{max} (µg/L)	t_{max}[a] (h)	AUC (µg*hr /L)	$t_{1/2}$ (h)	CL/F (L/h)	Vz/F (L)	C_{max}	AUC(0-∞)
LVAZ	Effect of rifampicin and ketoconazole on tadalafil PK	Open-label, random-ized	Part A Tadalafil 10 mg	12 HV	195 (28.5)	2.00	4017 (40.4)	16.7 (28.1)	2.49 (40.4)	60.0 (26.6)	rifampicin + tadalafil /tadalafil alone	
											0.54 (0.49,0.58)	0.12 (0.10,0.14)
			Part A Tadalafil 10 mg + rifampicin capsule 2 x 300 mg	11 HV	105 (28.1)	0.500	479 (22.4)	3.65 (15.1)	20.9 (22.4)	110 (22.2)		
			Part B Tadalafil 10 mg	12 HV	213 (20.7)	1.50	4005 (37.8)	15.9 (28.3)	2.50 (37.8)	57.4 (25.0)	ketoconazole + tadalafil /tadalafil alone	
											1.15 (1.06,1.25)	2.07 (1.71,2.51)
			Part B Tadalafil 10 mg + ketoconazole tablet 200 mg	11 HV	245 (16.7)	2.00	8442 (43.2)	30.4 (43.4)	1.18 (43.2)	51.9 (23.1)		

(continued)

Table 2.7.2.5.6. Summary of Pharmacokinetic Interaction Studies in Historic Studies (Continued)

Protocol Alias	Study Objectives	Study design	Treatment (Dose, Dosage formulation)	No. of Subjects for PK analysis	Geometric Mean (%CV) of PK parameter						Ratio of geometric least squares means (90%CI)	
					C_{max} (µg/L)	t_{max}[a] (h)	AUC (µg*hr /L)	$t_{1/2}$ (h)	CL/F (L/h)	Vz/F (L)	C_{max}	AUC(0-∞)
LVEV	Effect on tadalafil PK by ritonavir and ketoconazole	Open-label	Tadalafil 20 mg	16 HV	561.976 (23.2)	3.00	12850 (36.4)	16.4	1.56 (36.4)	36.9 (18.7)		
			Ritonavir capsule 2 x 100 mg + tadalafil	8 HV	533.887 (25.3)	4.00	33033 (40.3)	31.9	0.605 (40.3)	27.9 (24.2)	Tadalafil + ritonavir / tadalafil	
											0.980 (0.822, 1.17)	2.24 (1.86, 2.71)
			Tadalafil 20 mg	12 HV	548.156 (24.0)	3.00	13006 (43.9)	15.7	1.54 (43.9)	34.8 (24.7)		
			Ketoconazole tablet 2 x 200 mg + tadalafil	12 HV	669.731 (29.9)	4.00	53524 (49.2)	50.7	0.374 (49.2)	27.3 (32.3)	Tadalafil + ketoconazole / tadalafil	
											1.22 1.11 1.35	4.12 3.70 4.58

(continued)

Table 2.7.2.5.6. Summary of Pharmacokinetic Interaction Studies in Historic Studies (Continued)

Protocol Alias	Study Objectives	Study design	Treatment (Dose, Dosage formulation)	No. of Subjects for PK analysis	Geometric Mean (%CV) of PK parameter						Ratio of geometric least squares means (90%CI)	
					C_{max} (µg/L)	t_{max}[a] (h)	AUC (µg*hr /L)	$t_{1/2}$ (h)	CL/F (L/h)	Vz/F (L)	C_{max}	AUC(0-∞)
LVFV	Effect of ritonavir on tadalafil PK	Open-label, random-ized, 2 period, parallel	Tadalafil 20 mg	8 HV	320.459 (25.3)	3.50	7930 (37.2)	16.6	2.52 (37.2)	60.4 (19.1)	Tadalafil + ritonavir 500 mg / tadalafil alone	
											0.708 (0.572,0.877)	1.48 (1.23,1.77)
			Ritonavir capsule 5 x 100 mg + tadalafil	8 HV	226.915 (20.2)	3.00	11704 (26.5)	23.7	1.71 (26.5)	58.4 (24.6)		
			Tadalafil 20 mg	8 HV	297.158 (28.2)	1.00	7904 (31.6)	16.5	2.53 (31.6)	60.1 (26.2)	Tadalafil + ritonavir 600 mg / tadalafil alone	
											0.688 (0.555,0.852)	1.18 (0.982,1.41)
			Ritonavir capsule 6 x 100 mg + tadalafil	8 HV	204.412 (44.6)	1.50	9298 (34.4)	21.3	2.15 (34.4)	66.0 (37.8)		

(continued)

Table 2.7.2.5.6. Summary of Pharmacokinetic Interaction Studies in Historic Studies (Continued)

Protocol Alias	Study Objectives	Study design	Treatment (Dose, Dosage formulation)	No. of Subjects for PK analysis	Geometric Mean (%CV) of PK parameter						Ratio of geometric least squares means (90%CI)	
					C_{max} (µg/L)	t_{max}[a] (h)	AUC (µg*hr /L)	$t_{1/2}$ (h)	CL/F (L/h)	Vz/F (L)	C_{max}	AUC(0-∞)
LVAF	Effect on CYP3A4 substrate midazolam PK by single and multiple-dose Tadalafil Day 28 MD IC351 (Co-precipitate) 10 mg daily for 14 d + SD midazolam tablet 15 mg	Open-label	Day 15 SD tadalafil (Co-precipitate) 10 mg + SD midazolam tablet 15 mg	10 HV	midazolam PK data N=10							
					114 (43.4)	0.517	235 (51.7)	3.48 (50.2)	64.0 (51.7)	321 (38.4)	Midazolam + tadalafil (Day 15) / (mean of the first and second dose of midazolam).	
											1.02 (0.87, 1.20)	1.10 (0.98, 1.23)
			Day 28 tadalafil (Co-precipitate) 10 mg QD for 14 Days + midazolam tablet 15 mg	10 HV	117 (28.9)	0.500	185 (48.0)	3.02 (60.1)	81.0 (48.0)	353 (46.1)	Midazolam + tadalafil (Day 28) / (mean of the first and second dose of midazolam)	
											1.04 (0.87, 1.23)	0.87 (0.77, 0.98)

(continued)

Table 2.7.2.5.6. Summary of Pharmacokinetic Interaction Studies in Historic Studies (Continued)

Protocol Alias	Study Objectives	Study design	Treatment (Dose, Dosage formulation)	No. of Subjects for PK analysis	Geometric Mean (%CV) of PK parameter						Ratio of geometric least squares means (90%CI)	
					C_{max} (µg/L)	t_{max}[a] (h)	AUC (µg*hr /L)	$t_{1/2}$ (h)	CL/F (L/h)	Vz /F (L)	C_{max}	AUC(0-∞)
LVDM	Effect on CYP3A4 substrate, lovastatin PK by tadalafil single and multiple-dose	Open-label	Day 9 tadalafil 2 x 10 mg, QD 2days + SD lovastatin tablet 40 mg	16 HV	lovastatin PK data						Tadalafil + lovastatin (Day 9) / lovastatin (Day 1)	
					8.38 (43.6)	1.75	43.8 (66.6) (N=10)	-	-	-	1.10 (09.29, 1.30)	1.15 (0.995, 1.35)
			Day 21 tadalafil 2 x 10 mg QD 14 days + SD lovastatin tablet 40 mg	16 HV	8.82 (49.9)	2.00	34.4 (48.3) (N=9)	-	-	-	Tadalafil + lovastatin (Day 21) / lovastatin (Day 1)	
											1.16 (0.977, 1.37)	1.03 (0.884, 1.21)
			Day 35 tadalafil 2 x 10 mg + lovastatin tablet 40 mg	16 HV	8.93 (70.0)	2.50	44.1 (64.8) (N=10)	-	-	-	Tadalafil + lovastatin (Day 35) / lovastatin (Day 1)	
											1.17 (0.989, 1.39)	1.16 (0.989, 1.35)

(continued)

Table 2.7.2.5.6. Summary of Pharmacokinetic Interaction Studies in Historic Studies (Continued)

Protocol Alias	Study Objectives	Study design	Treatment (Dose, Dosage formulation)	No. of Subjects for PK analysis	Geometric Mean (%CV) of PK parameter						Ratio of geometric least squares means (90%CI)	
					C_{max} (mg/L)	t_{max}[a] (h)	AUC (mg*hr /L)	$t_{1/2}$ (h)	CL/F (L/h)	Vz/F (L)	C_{max}	AUC(0-∞)
LVAQ	Safety , tolerability, PD and PK interaction with warfarin	Double-blind, placebo-control-led, random-ized, 2-period crossover	Tadalafil placebo + (R)-warfarin 5 x 5 mg	12 HV males	Warfarin PK						Tadalafil + warfarin/ tadalafil placebo + warfarin	
					1.51 (19.6)	1.00	74.4 (16.2)	46.9 (14.5)	0.168 (16.2)	11.4 (12.0)	0.82 (0.72,0.92)	0.89 (0.85,0.93)
			Tadalafil 10 mg + (R)-warfarin 5 x 5 mg	12 HV males	1.23 (18.8)	1.50	65.9 (14.9)	44.9 (14.4)	0.190 (14.9)	12.3 (13.8)		
			Tadalafil placebo + (S)-warfarin 5 x 5 mg	12 HV males	1.56 (20.4)	1.00	56.6 (38.4)	35.6 (38.7)	0.221 (38.4)	11.4 (12.0)	Tadalafil + warfarin/ tadalafil placebo + warfarin	
											0.80 (0.69,0.92)	0.87 (0.80,0.94)
			Tadalafil 10 mg + (S)-warfarin 5 x 5 mg	12 HV males	1.25 (21.0)	1.00	49.3 (35.8)	34.0 (34.8)	0.254 (35.8)	12.5 (13.0)		

(continued)

Table 2.7.2.5.6. Summary of Pharmacokinetic Interaction Studies in Historic Studies (Continued)

Protocol Alias	Study Objectives	Study design	Treatment (Dose, Dosage formulation)	No. of Subjects for PK analysis	Geometric Mean (%CV) of PK parameter						Ratio of geometric least squares means (90%CI)	
					C_{max} (mg/L)	t_{max}[a] (h)	AUC (mg*hr /L)	$t_{1/2}$ (h)	CL/F (L/h)	Vz/F (L)	C_{max}	AUC(0-∞)
LVEX	Safety, tolerability, PD, and PK interaction with warfarin	Double-blind, placebo-control-led, random-ized, 2-period crossover	Tadalafil placebo + (R)-warfarin 5 x 5 mg	12 HV males	Warfarin PK						Tadalafil + warfarin/ tadalafil placebo + warfarin	
					1.40 (13.1)	1.00	71.1 (20.0)	45.7	0.176 (20.0)	11.6 (9.63)	0.963 (0.921,1.01)	0.930 (0.887,0.974)
			Tadalafil 20 mg + (R)-warfarin 5 x 5 mg	12 HV males	1.35 (16.1)	0.75	66.1 (19.2)	42.3	0.189 (19.2)	11.5 (11.5)		
			Tadalafil placebo + (S)-warfarin 5 x 5 mg	12 HV males	1.46 (15.1)	0.75	42.5 (21.5)	29.3	0.294 (21.5)	12.5 (12.7)	Tadalafil + warfarin/ tadalafil placebo + warfarin	
											0.961 (0.923,1.00)	0.917 (0.880,0.956)
			Tadalafil 20 mg + (S)-warfarin 5 x 5 mg	12 HV males	1.41 (16.7)	0.75	39.0 (24.0)	27.9	0.321 (24.0)	12.9 (13.4)		

(continued)

Table 2.7.2.5.6. Summary of Pharmacokinetic Interaction Studies in Historic Studies (Continued)

Protocol Alias	Study Objectives	Study design	Treatment (Dose, Dosage formulation)	No. of Subjects for PK analysis	Geometric Mean (%CV) of PK parameter						Ratio of geometric least squares means (90%CI)	
					C_{max} (µg/L)	t_{max}[a] (h)	AUC (µg*hr /L)	$t_{1/2}$ (h)	CL/F (L/h)	Vz/F (L)	C_{max}	AUC(0-∞)
LVAP	Safety, tolerability, PD, and PK interaction with theophylline	Double-blind, placebo-controlled, randomized, 4-period crossover	Tadalafil 10 mg + theophylline tablet (BID) (titration from 200 mg)	Theophylline PK							Tadalafil + theophylline/ tadalafil placebo + theophylline	
				14 HV	16.6[b] (14.2) (mg/L)	4.00	175[c] (13.7) (mg*hr /L)	-	3.12 (26.7)	-	0.982 (0.915,1.05)	0.978 (0.915,1.05)
			Tadalafil placebo + theophylline tablet (BID) (titration from 200 mg)	14 HV	16.7 [b] (22.8) (mg/L)	4.00	177 [c] (22.4) (mg*hr /L)	-	3.09 (31.8)	-		
LVAR	Tadalafil PK in Co-administration with tadalafil and Antacid, H2 antagonist	Open-label, randomized, 3-period crossover	Tadalafil 10 mg	12 HV	Tadalafil PK						-	
					196 (21.9)	2.00	4096 (30.8)	16.7 (25.6)	-	-	-	
			Tadalafil 10mg + H2 blocker (nizatidine)	12 HV	170 (20.9)	2.00	4088 (23.3)	17.2 (24.4)	-	-	Tadalafil 10mg + nizatidine/ tadalafil	
											0.86 (0.79,0.94)	1.00 (0.92,1.08)
			Tadalafil 10 mg + antacid (malox)	11 HV	139 (24.9)	4.00	3900 (29.6)	17.7 (27.6)	-	-	Tadalafil 10 mg + antacid/ tadalafil	
											0.70 (0.64,0.77)	0.94 (0.87,1.02)

(continued)

Table 2.7.2.5.6. Summary of Pharmacokinetic Interaction Studies in Historic Studies (Continued)

Protocol Alias	Study Objectives	Study design	Treatment (Dose, Dosage formulation)	No. of Subjects for PK analysis	Geometric Mean (%CV) of PK parameter						Ratio of geometric least squares means (90%CI)	
					C_{max} (µg/L)	t_{max}[a] (h)	AUC (µg*hr /L)	$t_{1/2}$ (h)	CL/F (L/h)	Vz/F (L)	C_{max}	AUC(0-∞)
LVAE	Safety, tolerability, PD, and effects on alcohol PK	Double-blind, placebo-controlled, randomized, 4-period crossover	Tadalafil 10 mg + alcohol 0.7 g/kg	16 HV males	Alcohol PK							
					79.3 (15.1) (mg/dL)	0.750	160 (12.7) $AUC_{(0-3)}$ (mg*h/dL)	-	-	-		
			Tadalafil placebo + alcohol 0.7 g/kg	16 HV males	76.6 (19.7) (mg/dL)	0.750	158 (9.46) $AUC_{(0-3)}$ (mg*h/dL)	-	-	-	Tadalafil + alcohol / tadalafil placebo +alcohol	
											1.04 (0.96, 1.12)	1.02 (0.966, 1.07)
LVET	Safety, tolerability, PD, and effects on alcohol PK	Double-blind, placebo-controlled, randomized, 3-period crossover	Tadalafil 20 mg + alcohol 0.7 g/kg	54 HV males	Tadalafil PK							
					349 (25.8)	3.08	5092 (23.2)	-	-	-		
			Tadalafil 20 mg + alcohol placebo 0.7 g/kg	54 HV males	356 (29.4)	1.94	5143 (29.2)	-	-	-		
			Tadalafil 20 mg + alcohol 0.7 g/kg	53 HV males	Alcohol PK							
					84 (15) (mg/dL)	0.83	127 (12.2) $AUC_{(0-2)}$ (mg*h/dL)	-	-	-		
			Tadalafil placebo + alcohol 0.7 g/kg	51 HV males	81 (15) (mg/dL)	0.83	121 (14.4) $AUC_{(0-2)}$ (mg*h/dL)	-	-	-		

(continued)

Table 2.7.2.5.6. Summary of Pharmacokinetic Interaction Studies in Historic Studies (Concluded)

Protocol Alias	Study Objectives	Study design	Treatment (Dose, Dosage formulation)	No. of Subjects for PK analysis	Geometric Mean (%CV) of PK parameter						Ratio of geometric least squares means (90%CI)	
					C_{max} (µg/L)	t_{max}[a] (h)	AUC (µg*hr /L)	$t_{1/2}$ (h)	CL/F (L/h)	Vz/F (L)	C_{max}	AUC (0-∞)
LVAV	Safety, tolerability, PD, and effect on the PK of Ca antagonist (amlodipine)	Double-blind, placebo-controlled, random ized, 2-period crossover	Tadalafil 10 mg + amlodipine 5 mg	18 HV	Amlodipine PK							
					9.34 (36.6)	8.00	174 [c] (37.8)	-	-	-		
			Tadalafil placebo + amlodipine 5 mg	17 HV	8.57 (31.3)	8.00	163 [c] (34.2)	-	-	-	Amlodipine + tadalafil / amlodipine + tadalafil placebo	
											1.06 (1.02, 1.10)	1.04[c] (0.994, 1.09)

Abbreviations: AUC = area under the concentration time curve from time 0 to infinity unless otherwise indicated.; C_{max} = maximal concentration; CI = confidence interval; CL/F = apparent clearance; CV = coefficient of variation; CYP = cytochrome P450; h = hours; HV = healthy volunteers; No. = number; PD = pharmacodynamics; PK = pharmacokinetics; $t_{1/2}$ = terminal half-life; t_{max} = time to maximal concentration; Vz/F = apparent volume of distribution.

[a] Median.

[b] C_{max} at steady state

[c] AUC(0-24)

Note: µg/L is equivalent to ng/mL.

Table 2.7.2.5.7. Index of Pharmacokinetic and Pharmacodynamic Studies and Analyses

Brief Description of Study	Trial Alias
Disposition and Metabolism Study	
[^{14}C]tadalafil (100 mg) single oral dose	**LVAA**
Healthy Subject PK, PD, and Tolerability	
First human dose, PK, safety, tolerability (5 mg)	**LVBS**
Mild to moderate renal impairment (10 mg)	**LVAJ**
End-stage renal failure (5, 10, 20 mg)	**LVDT**
Single & multiple-dose, PK, safety, tolerability (10 mg)	**LVAD**
Single & multiple-dose, PK (5, 10 mg)	**LVAU**
Multiple-dose, PK (10 and 20 mg)	**LVDK**
Single dose, PK, Japanese & Western origin (5, 10, 20, 40 mg)	**LVCS**
Multiple dose, PK (20 mg) Japanese	**LVCT**
RelBE, 3 tablet strengths, safety, tolerability, dose proportionality (2.5, 5, 10, 20 mg)	**LVBX**
Effect of Intrinsic Factors	
Elderly and young subjects, single and repeated dose (50 mg), safety, tolerability, PK	**LVBU**
Elderly subjects, SD/MD, safety, tolerability, PK, (10, 50, 100 mg)	**LVBH**
Elderly, single dose PK (10 mg)	**LVBW**
Single & multiple-dose, PK, safety, tolerability (10 mg)	**LVAD**
Single dose, PK in subjects of Japanese & Western origin (5, 10, 20, 40 mg)	**LVCS**
Single dose, PK in Chinese subjects (10, 20 mg)	**LVFU**
Diabetes, single dose (10 mg)	**LVAS**
Mild to moderate renal impairment (10 mg)	**LVAJ**
End-stage renal failure (5, 10, 20 mg)	**LVDT**
Hepatic impairment (10 mg)	**LVAK**
Effect of Other Drugs on Tadalafil PK	
Effect of rifampicin and ketoconazole	**LVAZ**
Effect of ketoconazole and ritonavir	**LVEV**

(continued)

Table 2.7.2.5.7. Index of Pharmacokinetic and Pharmacodynamic Studies and Analyses (Continued)

Brief Description of Study	Trial Alias
Effect of Other Drugs on Tadalafil PK (continued)	
Effect of ritonavir	**LVFV**
Effect of H_2-receptor antagonist and antacid	**LVAR**
Effect of oral contraceptives	**LVAG**
Effect of Tadalafil on PK of Other Drugs	
Effect of single and multiple tadalafil doses on midazolam	**LVAF**
Effect of single and multiple tadalafil doses on lovastatin	**LVDM**
Effect of tadalafil on theophylline	**LVAP**
Effect of tadalafil (10 mg) on warfarin	**LVAQ**
Effect of tadalafil (20 mg) on warfarin	**LVEX**
Metroprolol (β-blocker), patients with HT	**LVAW**
Effect of tadalafil (10 mg) on aspirin induced prolongation of bleeding time	**LVBV**
Effect of tadalafil (20 mg) on aspirin induced prolongation of bleeding time	**LVEY**
PK and/or PD Alcohol Interaction Studies	
10 mg tadalafil and alcohol	**LVAE**
20 mg tadalafil and alcohol	**LVDO**
20 mg tadalafil and alcohol	**LVET**
20 mg tadalafil and alcohol	**LVFS**
PD Nitrate Interaction Studies	
Hypotensive effect of SD/MD tadalafil (10 mg) on nitroglycerin	**LVAB**
Hypotensive effect of SD tadalafil (10 mg) on nitroglycerin	**LVCM**
Tadalafil and nitroglycerin or isosorbide mononitrate, patients with chronic stable angina	**LVBY**
Interaction with nitroglycerin in patients with coronary artery disease	**LVCP**
Interaction with nitroglycerin in healthy subjects & diabetic patients	**LVDN**

(continued)

Table 2.7.2.5.7. Index of Pharmacokinetic and Pharmacodynamic Studies and Analyses (Continued)

Brief Description of Study	Trial Alias
PD Alpha Blocker Interaction Studies	
Tamulosin (0.4 mg), tadalafil (10, 20 mg)	**LVAY**
Doxazosin (8 mg), tadalafil (20 mg)	**LVFG**
Doxazosin (1, 2, 4, and 8 mg), tadalafil (20 mg)	**LVFT**
Tamulosin (0.4 mg), tadalafil (5 mg)	**LVGN**
Doxazosin (1, 2, and 4 mg), tadalafil (5 mg)	**LVGT**
PD Antihypertensive Interaction Studies	
Metroprolol (SR; 25 to 200 mg), tadalafil (10 mg), patients with HT	**LVAW**
Bendrofluazide (2.5 mg) tadalafil (20 mg), patients with HT	**LVAX**
Enalapril (total daily dose between 10 and 20 mg), tadalafil (10 mg), patients with HT	**LVBC**
Amlodipine, (5 mg), tadalafil (10 mg), HS	**LVAV**
Amlodipine (5 mg), tadalafil, (20 mg), HS	**LVDP**
Angiotensin II AT1 receptor antagonists, tadalafil, (20 mg), patients with HT	**LVDS**
Antihypertensive agents (2, 3 or 4 classes), tadalafil, (20 mg), patients with HT	**LVDV**
PD Anticoagulant Interaction Studies	
Effect of (10 mg) tadalafil on aspirin induced prolongation of bleeding time	**LVBV**
Effect of (20 mg) tadalafil on aspirin induced prolongation of bleeding time	**LVEY**
Effect of tadalafil (10 mg) on PK, PD of warfarin	**LVAQ**
Effect of tadalafil (20 mg) on PK, PD of warfarin	**LVEX**
Thorough QT Interval Study	
Effect of tadalafil (100 mg) on QT interval	**LVFB**
Special Studies	
Effect of tadalafil on visual function, single oral dose	**LVAN**
Effects on color vision	**LVCN**
Effect of tadalafil on visual function	**LVFF**
Renal plasma flow, lumbar & gluteal venocongestion	**LVFA**

(continued)

Table 2.7.2.5.7. Index of Pharmacokinetic and Pharmacodynamic Studies and Analyses (Concluded)

Brief Description of Study	Trial Alias
Special Studies (continued)	
Tadalafil and nitroglycerin or isosorbide mononitrate, patients with chronic stable angina	**LVBY**
Interaction with nitroglycerin in patients with coronary artery disease	**LVCP**
Theophylline, hemodynamic effects	**LVAP**
Effect on myocardial perfusion using PET	**LVBZ**
Brief Description of Study	Trial Alias
Phase 3 Studies Providing Population PK and/or PD Information	
Once daily, patients with ED (2.5 and 5 mg)	**LVFP**
On demand, patients with ED, efficacy and safety	**LVDJ/LVDI**
On demand, patients with ED, efficacy and safety	**LVCE**

Abbreviations: HS = healthy subjects; HT = hypertension; MD = multiple dose; PD = pharmacodynamics; PET = positron emission tomography; PK = pharmacokinetics; RelBE = relative bioequivalence; SD = single dose.