Table of Contents

Section **Page**

Table of Contents

Table **Page**

2.7.1.4. Appendix

Table APP.2.7.1.1. Summary of LC/MS/MS Bioanalytical Methods

Study Alias	Matrix	Analytes	Sensitivity of Method/Range	Accuracy (relative error) intra/inter assay	Precision (relative standard deviation) intra/inter assay
LVHO	Plasma	Tadalafil	[redacted]		
LVHC	Plasma	Tadalafil			
	Plasma	Total methylcatechol metabolite			
LVGZ	Plasma	Tadalafil			
	Plasma	Methylcatechol metabolite			
	Plasma	Total methylcatechol metabolite			
	Plasma	Bosentan and bosentan metabolites Ro 47-8634, Ro 48-5033, and Ro 64-1056			
LVHL	Serum	Digoxin			
	Urine	Digoxin			
LVHM	Plasma	Tadalafil			
	Plasma	Total methylcatechol metabolite			
	Plasma	Ethinylestradiol			
	Plasma	Ethinylestradiol sulfate			
	Plasma	Levonorgestrel			
LVGY	Plasma	Tadalafil			

Abbreviations: LC/MS/MS = liquid chromatography with tandem mass spectrometry; methylcatechol = unconjugated methylcatechol metabolite of tadalafil; total methylcatechol = sum of free methylcatechol and the glucuronide conjugate of methylcatechol.

Note: µg/L is equivalent to ng/mL

Table APP.2.7.1.2. Summary of Bioavailability, Bioequivalency 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(0-∞) (µg*h/L)	$t_{1/2}$ (h)	CL/F (L/h)	Vz/F (L)	C_{max}	AUC(0-∞)
LVAH	Comparison of the safety, tolerability, and PK of the 3 formulations	Open-label, balanced, randomized, 3-period crossover study	tadalafil (Co-precipitate tablet) 10 mg	HS: 18 M: 18 F: 0	158 [redacted]	3.52	3936 [redacted]	16.0 [redacted]	2.54 [redacted]	58.5 [redacted]	Market Image tablet/Co-precipitate	
											1.27 (1.12, 1.45)	0.957 (0.889, 1.03)
			tadalafil (Market Image tablet) 10 mg		202 [redacted]	2.00	3767 [redacted]	16.1 [redacted]	2.65 [redacted]	61.6 [redacted]	[redacted]	
			[redacted]									

Note: µg/L is equivalent to ng/mL

(continued)

Table APP.2.7.1.2. Summary of Bioavailability, Bioequivalency 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(0-∞) (µg*h/L)	$t_{1/2}$ (h)	CL/F (L/h)	Vz/F (L)	C_{max}	AUC(0-∞)
LVBX	Relative bioavailability and PK of 3 dose strengths	Single-blind, randomized, 3-period crossover study (Part A), 4-period crossover study (Part B) Parts A & B: Market Image tablet	A	4 x 2.5 mg	HS: 24 M: 12 F: 12	190 [redacted]	2.00	4120 [redacted]	18.0 [redacted]	2.43 [redacted]	63.0 [redacted]	4 x 2.5 mg tablet/1 x 10 mg tablet	
												1.03 (0.96, 1.10)	1.03 (0.97, 1.09)
				2 x 5 mg		196 [redacted]	2.00	4071 [redacted]	17.7 [redacted]	2.46 [redacted]	62.9 [redacted]	2 x 5 mg tablet/1 x 10 mg tablet	
												1.06 (0.99, 1.14)	1.02 (0.96, 1.08)
				1 x 10 mg		184 [redacted]	2.00	4005 [redacted]	17.6 [redacted]	2.50 [redacted]	63.5 [redacted]	—	—
			B	1 x 2.5 mg	HS: 16 M: 8 F: 8	51.6 [redacted]	1.01	900 [redacted]	16.5 [redacted]	2.78 [redacted]	66.0 [redacted]	—	—
				1 x 5 mgb		103 [redacted]	2.00	1888 [redacted]	17.3 [redacted]	2.65 [redacted]	66.0 [redacted]	—	—
				1 x 10 mgb		190 [redacted]	2.00	3647 [redacted]	16.7 [redacted]	2.74 [redacted]	66.1 [redacted]	—	—
				2 x 10 mg		322 [redacted]	3.00	6809 [redacted]	16.7 [redacted]	2.94 [redacted]	70.9 [redacted]	—	—

Note: µg/L is equivalent to ng/mL

(continued)

Table APP.2.7.1.2. Summary of Bioavailability, Bioequivalency 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(0-∞) (µg*h/L)	$t_{1/2}$ (h)	CL/F (L/h)	Vz/F (L)	C_{max}	AUC(0-∞)
[redacted]												
LVDL	Relative bioavailability of 2 dose strengths	Open-label, randomized, 2 period, crossover study	tadalafil (Market Image tablet) 1 x 20 mg	HS: 20 M: 20 F: 0	351 [redacted]	2.00	8383 [redacted]	18.1 [redacted]	2.39 [redacted]	62.1 [redacted]	1 x 20 mg/2 x 10mg	
											1.01 (0.940, 1.09)	1.02 (0.941, 1.11)
			tadalafil (Market Image tablet) 2 x 10 mg		346 [redacted]	3.00	8192 [redacted]	18.0 [redacted]	2.44 [redacted]	63.4 [redacted]	—	—

Note: µg/L is equivalent to ng/mL

(continued)

Table APP.2.7.1.2. Summary of Bioavailability, Bioequivalency Studies (Concluded)

Protocol Alias	Study Objectives	Study design	Treatment (Dose, Dosage formulation) [b]	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(0-∞) (µg*h/L)	$t_{1/2}$ (h)	CL/F (L/h)	Vz/F (L)	C_{max}	AUC(0-∞)
LVBT	Relative bioavailability of coprecipitate tablets relative to the oral suspension	Open-label, 3-way, crossover study design	tadalafil 100 mg as 50 ml oral suspension fasted	HS: 13 M: 13 F: 0	909[c] [redacted]	5	28348[c] [redacted]	20.6[c] [redacted]	NR	NR	Fasted tablets/fasted suspension 0.68 (0.49, 0.87)	0.86 (0.63, 1.47)
			tadalafil 100 mg 2 x 50 mg tablets fasted		612[c] [redacted]	5	27369[c] [redacted]	28.9[c] [redacted]	NR	NR	Fed tablets/fasted tablets 2.10 (1.48, 3.45)	1.43 (0.84, 2.36)
			tadalafil 100 mg 2 x 50 mg tablets fed		1235[c] [redacted]	8	39379[c] [redacted]	19.1[c] [redacted]	NR	NR	—	—

Abbreviations: AUC(0-∞) = area under the concentration time curve from time 0 to infinity; C_{max} = maximal concentration; CI = confidence interval; CL/F = apparent clearance; CV = coefficient of variation; F = females; HS = healthy subjects; M = males; No. = number; NR = not reported; PK = pharmacokinetics; $t_{1/2}$ = terminal half-life; t_{max} = time to maximal concentration; Vz/F = apparent volume of distribution.

[a] Median.

[b] Oral suspension fed, NPK=13 subjects; Tablet NPK=11 subjects.

[c] Parameters were measured with arithmetic mean.

Note: µg/L is equivalent to ng/mL.

Table APP.2.7.1.3. Summary of Pharmacokinetics Study (Food Effect)

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(0-∞) (µg*h/L)	$t_{1/2}$ (h)	CL/F (L/h)	Vz/F (L)	C_{max}	AUC(0-∞)
LVAL	Food effect on tadalafil PK	Open-label, randomized, 2-period, crossover study	Market Image tablet 10 mg fed	HS: 16 M: 8 F: 8	210 [redacted]	2.10	4905 [redacted]	17.7 [redacted]	2.04 [redacted]	52.2 [redacted]	fed/fasted	
											0.96 (0.82, 1.13)	0.95 (0.84, 1.07)
			Market Image tablet 10 mg fasted		219 [redacted]	2.17	5181 [redacted]	18.5 [redacted]	1.93 [redacted]	51.6 [redacted]	—	—
LVDQ	Food effect on tadalafil PK	Open-label, randomized, 2-period, crossover study	Market Image tablet 20 mg fed	HS: 18 M: 4 F: 14	345 [redacted]	2.50	6943 [redacted]	17.0 [redacted]	2.88 [redacted]	70.7 [redacted]	fed/fasted	
											1.16 (1.07, 1.26)	1.08 (1.02, 1.15)
			Market Image tablet 20 mg fasted		297 [redacted]	2.00	6419 [redacted]	17.3 [redacted]	3.12 [redacted]	77.6 [redacted]	—	—
LVAI	Food effect on tadalafil PK	Open-label, balanced, randomized, 3-period, crossover study	Market Image tablet 10 mg fed evening	HS: 12 M: 12 F: 0	194 [redacted]	3.00	4490 [redacted]	16.2 [redacted]	2.23 [redacted]	52.1 [redacted]	fed/fasted	
											1.03 (0.923, 1.15)	1.15 (1.04, 1.28)
			Market Image tablet 10 mg, fasted evening		188 [redacted]	2.00	3894 [redacted]	16.7 [redacted]	2.57 [redacted]	61.7 [redacted]	evening/morning	
											0.793 (0.711, 0.885)	0.810 (0.727, 0.903)
			Market Image tablet 10 mg, fasted morning		237 [redacted]	2.00	4806 [redacted]	17.2 [redacted]	2.08 [redacted]	51.8 [redacted]	—	—

Note: µg/L is equivalent to ng/mL

(continued)

Table APP.2.7.1.3. Summary of Pharmacokinetics Study (Food Effect) (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(0-∞) (µg*h/L)	$t_{1/2}$ (h)	CL/F (L/h)	Vz/F (L)	C_{max}	AUC(0-∞)
LVHO	Food effect on tadalafil PK	Open-label randomized 2-period crossover study	40 mg fed 2 x 20 mg	HS: 13 M: 7 F: 6	586 [redacted]	3.00	17386 [redacted]	20.7 [redacted]	2.31 [redacted]	68.8 [redacted]	fed/fasted	
											1.07 (0.994, 1.15)	1.14 (1.05, 1.22)
			40 mg fasted 2 x 20 mg	HS: 14 M: 9 F: 5	553 [redacted]	2.00	15404 [redacted]	20.2 [redacted]	2.59 [redacted]	75.6 [redacted]	—	—

Abbreviations: AUC(0-∞) = area under the concentration time curve from time 0 to infinity; C_{max} = maximal concentration; CI = confidence interval; CL/F = apparent clearance; CV = coefficient of variation; F = females; HS = healthy subjects; M = males; No. = number; NR = not reported; 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 APP.2.7.1.4. Summary of Clinical Trial Tablet Lots Used in Clinical Studies Supporting the PAH Submission

Dose Form Strength	Clinical Protocol Number	Dose Form Lot Number	Batch Size (Tablets)	Date of Manufacture	Place of Manufacture	Drug Substance Lot Number
20 mg	LVGZ	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.5 mg	LVGY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.5 mg	LVGY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 mg	LVGY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 mg	LVGY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20 mg	LVGY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20 mg	LVGY	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20 mg	LVGX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20 mg	LVGX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20 mg	LVGX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20 mg	LVHC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20 mg	LVHO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20 mg	LVHM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20 mg	LVHL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table APP.2.7.1.5. Clinical Study Codes with Corresponding Clinical Trial Material Lot Numbers

Protocol Number	Country of Study Site	Package	Package Lot Number	Dose Form Lot Number	Dose Form/ Strength (mg)
H6D-MC-LVGZ	United Kingdom	Blister	[redacted]	[redacted]	Tablets/20 mg
H6D-MC-LVGY	Japan	Blister	[redacted]	[redacted]	Tablets/2.5 mg Tablets/PTM Tablets/10 mg Tablets/PTM Tablets/20 mg Tablets/PTM
	United States Ireland Belgium Germany Canada Spain France United Kingdom Italy	Blister	[redacted]	[redacted]	Tablets/2.5 mg Tablets/10 mg Tablets/20 mg Tablets/PTM Tablets/PTM Tablets/PTM Tablets/2.5 mg Tablets/PTM Tablets/10 mg Tablets/20 mg Tablets/PTM Tablets/PTM Tablets/2.5 mg Tablet/PTM Tablets/10 mg Tablet/PTM Tablet/20 mg Tablets/PTM
	US	Blister	[redacted]	[redacted]	Tablet/2.5 mg Tablets/PTM Tablet/10 mg Tablet/20 mg Tablet/PTM Tablet/PTM

(continued)

Table APP.2.7.1.5. Clinical Study Codes with Corresponding Clinical Trial Material Lot Numbers (Continued)

Protocol Number	Country of Study Site	Package	Package Lot Number	Dose Form Lot Number	Dose Form/ Strength (mg)
H6D-MC-LVGX	Japan	Blister	[redacted]	[redacted]	Tablets/20 mg Tablets/PTM Tablets/PTM Tablets/20 mg
	United States	Blister	[redacted]	[redacted]	Tablets/20 mg Tablets/PTM Tablets/20 mg Tablets/PTM Tablets/20 mg Tablets/PTM Tablets/20 mg Tablets/PTM Tablets/20 mg Tablets/PTM Tablets/20 mg Tablets/PTM Tablets/20 mg Tablets/PTM Tablets/20 mg Tablets/PTM
	United States Canada	Bottle	[redacted]	[redacted]	Tablets/20 mg Tablets/20 mg
	Belgium Germany Spain France United Kingdom Ireland Italy Canada	Blister	[redacted]	[redacted]	Tablet/20 mg Tablets/PTM Tablets/20 mg Tablets/PTM Tablets/20 mg Tablets/PTM Tablets/20 mg Tablets/PTM Tablets/20 mg Tablets/PTM Tablets/20 mg Tablets/PTM
	Belgium Germany Spain France United Kingdom Ireland Italy	Bottle	[redacted]	[redacted]	Tablets/20mg

(continued)

Table APP.2.7.1.5. Clinical Study Codes with Corresponding Clinical Trial Material Lot Numbers (Concluded)

Protocol Number	Country of Study Site	Package	Package Lot Number	Dose Form Lot Number	Dose Form/ Strength (mg)
H6D-MC-LVHC	Japan	Bottle	[redacted]	[redacted]	Tablets/20 mg Tablets/PTM
H6D-EW-LVHO	United Kingdom	Blister	[redacted]	[redacted]	Tablets/20 mg
H6D-EW-LVHL	United Kingdom	Blister	[redacted]	[redacted]	Tablets/20 mg
H6D-EW-LVHM	United Kingdom	Bottle	[redacted]	[redacted]	Tablets/20 mg Tablets/PTM

Abbreviation: PTM = Placebo to match