

Summary ID# 10077

Clinical Study Summary: Study H6D-MC-LVGU

A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study Evaluating the Efficacy and Safety of Tadalafil (5 mg and 20 mg) Administered Once Daily to Subjects with Mild to Moderate Hypertension

Date summary approved by Lilly: 14 June 2007

Brief Summary of Results

The primary objectives of this Phase 2 study were to evaluate the efficacy of tadalafil 5 mg and 20 mg compared with placebo when taken once daily for 8 weeks, as determined by the change from baseline in cuff seated trough diastolic blood pressure in subjects with mild to moderate hypertension and to assess the safety of tadalafil 5 mg and 20 mg taken once daily for 8 weeks in subjects with mild to moderate hypertension. The results of the study are as follows:

Efficacy

- *Cuff seated trough blood pressures:*

Diastolic: Mean placebo-adjusted reductions in cuff seated diastolic blood pressure were -4.3 mm Hg with tadalafil 5 mg ($p=.002$) and -5.3 mm Hg with tadalafil 20 mg ($p<.001$).

Systolic: Mean placebo-adjusted reductions in cuff seated systolic blood pressure were -3.5 mm Hg with tadalafil 5 mg ($p=.047$) and -3.6 mm Hg with tadalafil 20 mg ($p=.047$).

- *24-hour ambulatory blood pressures:*

Mean placebo-adjusted reductions in 24-hour ambulatory diastolic blood pressure were statistically significant for both tadalafil 5 mg (-3.8 mm Hg; $p=.003$) and tadalafil 20 mg (-4.7 mm Hg; $p=.001$).

Mean placebo-adjusted reductions in 24-hour ambulatory systolic blood pressure were statistically significant for tadalafil 20 mg (-6.0 mm Hg;

p=.005), while not statistically significant for tadalafil 5 mg (-3.4 mm Hg; p=.062).

- *Number of subjects attaining “blood pressure control” of <140/90 mm Hg:*

Once daily administration of tadalafil 5 mg or 20 mg for 8 weeks did not lead to statistically significant improvement (compared with placebo) in the number of subjects attaining blood pressures <140/90 mm Hg (i.e., systolic <140 mm Hg and diastolic <90 mm Hg).

Safety

- No deaths or treatment-related serious adverse events (SAEs) were reported during the study.
- The incidence of discontinuation due to adverse events (AEs) was less than 10% for each treatment group.
- Most treatment-emergent adverse events (TEAEs) were mild or moderate in intensity and were experienced by ≤8 subjects each.
- 15.6% of subjects experienced AEs that were considered to be related to study drug during the double-blind treatment and follow-up periods.
- No clinically meaningful changes were observed by the Sponsor for laboratory values, heart rate, or electrocardiogram (ECG) variables for any treatment group.

Title of Study: A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study Evaluating the Efficacy and Safety of Tadalafil (5 mg and 20 mg) Administered Once Daily to Subjects with Mild to Moderate Hypertension	
Investigators: This multicenter study included 25 principal investigators.	
Study Centers: This study was conducted at 25 study centers in one country.	
Length of Study: 9 months Date of first subject visit: 08 September 2005 Date of last subject completed: 15 June 2006	Phase of Development: 2
Objectives: <u>Primary:</u> <ul style="list-style-type: none"> To evaluate the efficacy of tadalafil 5 mg and 20 mg compared with placebo, when taken once daily for 8 weeks, as determined by the change from baseline in cuff seated trough diastolic blood pressures in subjects with mild to moderate hypertension. To assess the safety of tadalafil 5 mg and 20 mg taken once daily for 8 weeks in subjects with mild to moderate hypertension. <u>Secondary:</u> <ul style="list-style-type: none"> To evaluate the efficacy of tadalafil 5 mg and 20 mg compared with placebo, when taken once daily for 8 weeks, as determined by the change from baseline in cuff seated trough systolic blood pressures. To evaluate the efficacy of tadalafil 5 mg and 20 mg compared with placebo, when taken once daily for 8 weeks, as determined by the ambulatory systolic and diastolic blood pressures. To determine the duration and consistency of the reduction in blood pressure, relative to placebo, after 8 weeks of treatment with tadalafil 5 mg and 20 mg when taken once daily as measured by trough-to-peak (T/P) ratio of the 24-hour ambulatory systolic and diastolic blood pressures. To characterize the efficacy of tadalafil 5 mg and 20 mg compared with placebo, when taken once daily for 8 weeks, in achieving blood-pressure control, as determined by the percentage of subjects with trough ambulatory or cuff seated blood pressures <140/90 mm Hg at the end of the treatment period (8 weeks). 	
Study Design: This was a multicenter, randomized, double-blind, parallel-group, and placebo-controlled study to evaluate the efficacy and safety of tadalafil 5 mg and 20 mg administered once daily for 8 weeks in subjects with mild to moderate hypertension. Enrolled subjects discontinued current antihypertensive medications and began a 4-week, single-blind, placebo lead-in period, after which they were randomly assigned to tadalafil 5 mg, tadalafil 20 mg, or placebo for the 8-week double-blind treatment period. Subjects who completed the treatment period entered a 2-week follow-up period. The duration of the study was approximately 14 weeks. The study design is schematically represented in Figure LVGU.1.	
Number of Subjects: Planned: Approximately 171 subjects, 57 subjects per treatment group (114 tadalafil, 57 placebo). Randomized: 62 tadalafil 5 mg, 57 tadalafil 20 mg, and 61 placebo. Completed Treatment Period: 50 tadalafil 5 mg, 52 tadalafil 20 mg, 46 placebo. Completed Protocol: 50 tadalafil 5 mg, 47 tadalafil 20 mg, 44 placebo.	
Diagnosis and Main Criteria for Inclusion: Subjects were at least 18 years of age, had a documented medical history of hypertension, and met the following criteria for hypertension: an average of 3 sitting diastolic blood pressure measurements at Visit 1 of >80 to ≤104 mm Hg (subjects treated for hypertension) or ≥95 to ≤104 mm Hg (subjects not treated for hypertension), and baseline cuff seated diastolic blood pressure ≥95 to ≤104 mm Hg, determined as the average of triplicate measurements at Visit 3 and Visit 4.	
Test Product, Dose, and Mode of Administration: Tadalafil 5 mg or 20 mg, given orally once a day during the treatment period.	

Reference Therapy, Dose, and Mode of Administration:

Placebo, given orally once a day to all subjects during the 4-week lead-in period. Subjects randomly assigned to placebo treatment received placebo orally once daily for an additional 8 weeks during the treatment period.

Duration of Treatment: 8 weeks for tadalafil; 12 weeks for placebo

Variables:**Primary Efficacy:**

- Mean change from baseline in cuff seated trough diastolic blood pressure after 8 weeks of treatment.

Secondary Efficacy:

- Change from baseline in cuff seated trough systolic blood pressures after 8 weeks of treatment.
- Change from baseline in ambulatory systolic and diastolic blood pressures after 8 weeks of treatment.
- Change from baseline in T/P ratio of the 24-hour ambulatory systolic and diastolic blood pressures after 8 weeks of treatment.
- Percentage of subjects with trough ambulatory blood pressures <140/90 mm Hg after 8 weeks of treatment.
- Percentage of subjects with trough cuff seated blood pressures <140/90 mm Hg after 8 weeks of treatment.

Safety:

- Adverse events (AEs), changes in clinical laboratory values, electrocardiograms (ECGs), and vital signs.

Evaluation Methods:Statistical:

Subjects were randomly assigned to 1 of 3 treatment groups (tadalafil 5 mg, tadalafil 20 mg, or placebo) in a 1:1:1 ratio stratified by baseline diastolic blood pressure category (95 to 99 mm Hg or 100 to 104 mm Hg) and race (Black/African American or non-Black/non-African American). The planned population (171 randomized subjects [57 subjects per treatment group]) was estimated to provide 80% power at α -level (1-sided) of .05. No adjustment was planned for multiple comparisons. Statistical analyses included randomized subjects who received any double-blind study medication (tadalafil or placebo). Descriptive summary statistics were presented for the primary endpoint and key secondary endpoints by the stratification factors.

An analysis of variance (ANOVA) model, stratified by the randomization strata, was used for the analysis of the primary efficacy endpoint (change in cuff seated trough diastolic blood pressure). For secondary efficacy endpoints, change in cuff seated trough systolic blood pressure and change in ambulatory systolic and diastolic blood pressures were analyzed in the same manner as the primary endpoint. Mean T/P ratio of the 24-hour ambulatory systolic and diastolic blood pressures was analyzed using a stratified Wilcoxon rank-sum test. The percentage of subjects achieving blood pressure control at Week 8 (trough [average of hourly mean at 23rd and 24th hours postdose] ambulatory or cuff seated blood pressures <140/90 mm Hg) were assessed using a Cochran-Mantel-Haenszel (CMH) test stratified by the randomization strata of baseline diastolic blood pressure and race. Safety was assessed for all treatment groups.

Study Design

The study design is represented schematically in Figure LVGU.1.

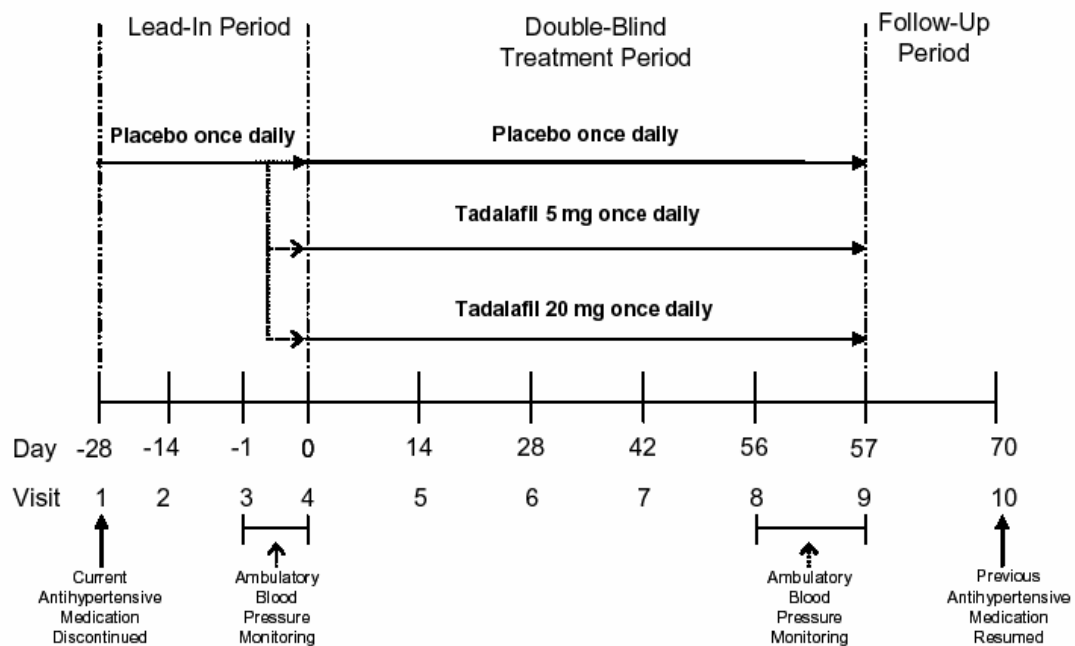


Figure LVGU.1. Study design.

Results

Subject Demographics

Table LVGU.1 summarizes baseline demographic characteristics for the full analysis population. The full analysis population was defined as subjects who were randomly assigned to treatment, received any study drug during the double-blind treatment period, and were not found to be ineligible for the study at a later date. This population was based on the intent-to-treat (ITT) principle and was used for efficacy analyses. Subjects in the full analysis population were analyzed by assigned treatment regardless of the treatment that was actually received.

All treatment groups in the full analysis population which included 167 subjects (55 placebo, 57 tadalafil 5 mg, and 55 tadalafil 20 mg) were well balanced for age, weight, height, and body mass index at baseline. The mean age of subjects was 53.1 years, and most subjects were male, Caucasian, and had no history of erectile dysfunction. All treatment groups were well balanced for baseline hypertension characteristics.

Table LVGU.1. Subject Demographics and Baseline Characteristics

Demographic Variables	Treatment			Total (N = 167)
	Placebo (N = 55)	Tadalafil 5 mg (N = 57)	Tadalafil 20 mg (N = 55)	
Age (years), Mean (SD)	53.9 (10.41)	52.6 (11.73)	52.9 (10.44)	53.1 (10.84)
Age (years) Category, n (%)				
<65	46 (83.6)	50 (87.7)	51 (92.7)	147 (88.0)
≥65	9 (16.4)	7 (12.3)	4 (7.3)	20 (12.0)
≥75	3 (5.5)	1 (1.8)	1 (1.8)	5 (3.0)
Sex, n (%)				
Male	34 (61.8)	42 (73.7)	34 (61.8)	110 (65.9)
Female	21 (38.2)	15 (26.3)	21 (38.2)	57 (34.1)
Ethnicity, n (%)				
Hispanic	10 (18.2)	5 (8.8)	13 (23.6)	28 (16.8)
Non-Hispanic	45 (81.8)	52 (91.2)	42 (76.4)	139 (83.2)
Race, n (%)				
American Indian or Alaska Native	0	1 (1.8)	0	1 (0.6)
Asians	0	1 (1.8)	0	1 (0.6)
Black/African American	17 (30.9)	18 (31.6)	16 (29.1)	51 (30.5)
White	38 (69.1)	37 (64.9)	39 (70.9)	114 (68.3)
Height (cm), Mean (SD)	169.7 (12.84)	174.5 (9.31)	170.6 (10.74)	171.6 (11.18)
Weight (kg), Mean (SD)	87.1 (16.81)	90.1 (13.45)	89.1 (14.82)	88.8 (15.03)
Body Mass Index (kg/m ²), Mean (SD)	30.0 (3.04)	29.6 (3.49)	30.4 (2.82)	30.0 (3.13)
Currently Consume Alcohol, n (%)				
No	36 (65.5)	29 (50.9)	26 (47.3)	91 (54.5)
Currently Exercise Regularly, n (%)				
No	25 (45.5)	36 (63.2)	33 (60.0)	94 (56.3)
Currently on Restricted Diet, n (%)				
No	36 (65.5)	52 (91.2)	41 (74.5)	129 (77.2)

(Continued)

Table LVGU.1. Subject Demographics and Baseline Characteristics (Concluded)

Demographic Variables	Treatment			Total (N = 167)
	Placebo (N = 55)	Tadalafil 5 mg (N = 57)	Tadalafil 20 mg (N = 55)	
History of ED				
No	17 (30.9)	26 (45.6)	17 (30.9)	60 (35.9)
Etiology of ED, n (%)				
Psychogenic	0	0	2 (3.6)	2 (1.2)
Organic	4 (7.3)	4 (7.0)	5 (9.1)	13 (7.8)
Mixed	0	2 (3.5)	3 (5.5)	5 (3.0)
Unknown	12 (21.8)	9 (15.8)	6 (10.9)	27 (16.2)
Duration of ED, n (%)				
<3 Months	1 (1.8)	0	0	1 (0.6)
≥3 months to <6 months	0	1 (1.8)	0	1 (0.6)
≥6 months to <1 year	3 (5.5)	1 (1.8)	0	4 (2.4)
≥1 year	12 (21.8)	12 (21.1)	16 (29.1)	40 (24.0)
Hypertension Characteristics				
Duration of Hypertension ^a (years), Mean (SD)	8.30 (7.76)	7.85 (8.308)	6.93 (5.386)	7.70 (7.255)
Antihypertensive Therapy at Screening, n (%)				
Yes	42 (76.4)	38 (66.7)	38 (69.1)	118 (70.7)
Baseline Diastolic BP (mm Hg) ^b , Mean (SD)	98.2 (2.16)	98.1 (2.37)	98.0 (2.07)	98.1 (2.20)
Baseline Systolic BP (mm Hg), Mean (SD)	147.5 (12.63)	147.0 (13.36)	149.6 (10.37)	148.0 (12.18)

Abbreviations: BP = blood pressure, ED = erectile dysfunction, N = number of subjects, n = subjects with nonmissing data at baseline and endpoint, SD = standard deviation.

^a Number of years from the diagnosis date to the informed consent date.

^b Baseline is the average of the mean blood pressure measurements at Visit 3 and Visit 4.

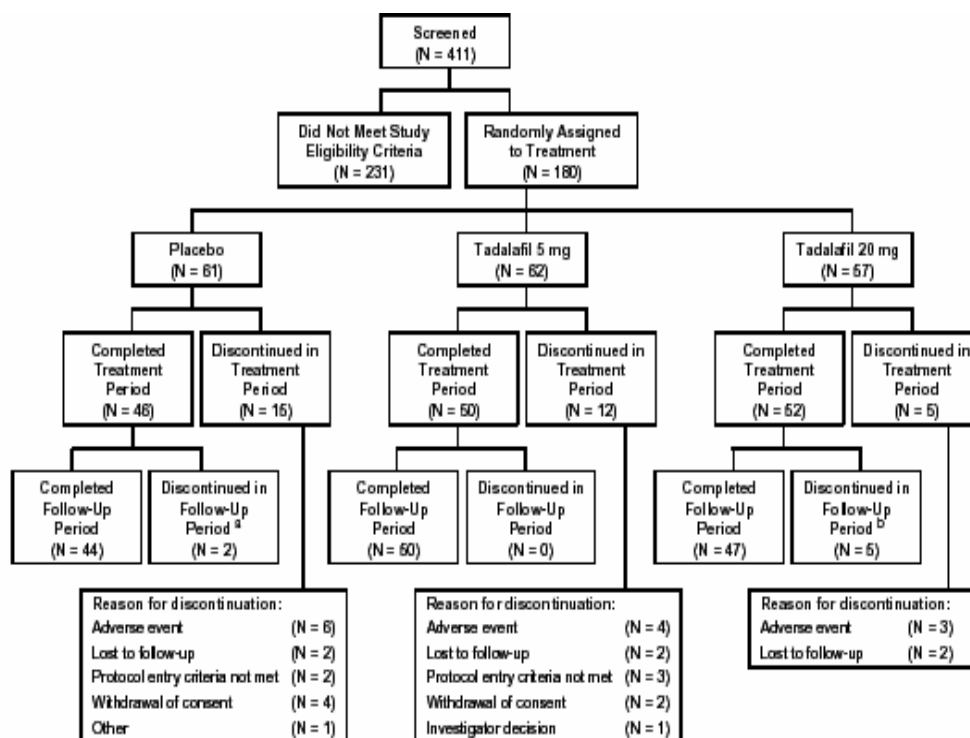
Subject Disposition

A total of 231 subjects did not meet eligibility requirements prior to being randomized and assigned to treatment; the most frequently reported reasons that subjects were not randomly assigned to treatment included inability to meet protocol entry criteria (153 subjects, 66.2%) and withdrawal of consent (37 subjects, 16.0%).

Of the 180 subjects who were randomly assigned to treatment, 61 were assigned to placebo, 62 were assigned to tadalafil 5 mg, and 57 were assigned to tadalafil 20 mg. Most subjects who were randomly assigned to treatment completed the treatment period: 148 subjects (82.2%). Among the 32 subjects who discontinued prior to completing the

treatment period, 13 discontinued due to adverse events [(AEs); 6 placebo, 4 tadalafil 5 mg, and 3 tadalafil 20 mg], 6 withdrew consent, and 6 were lost to follow-up. Additionally, 7 subjects discontinued prior to completion of the 2-week follow-up period.

Figure LVGU.2. presents the disposition of all subjects who were screened for this study.



Abbreviations: N = total number of subjects.

^a Reason: Withdrawal of consent (N = 2).

^b Reason: Lost to follow-up (N=1), Withdrawal of consent (N=1), Other (N=3).

Figure LVGU.2. Subject disposition.

Primary Efficacy Measure

Changes in Cuff Seated Trough Diastolic Blood Pressure from Baseline to Endpoint

The primary efficacy measure was the mean change from baseline in cuff seated trough diastolic blood pressure after 8 weeks of treatment. Cuff seated trough diastolic blood pressure was calculated as the mean of 3 measurements taken at each visit. Baseline was defined as the average of the Visit 3 and Visit 4 (Study Days -1 and 0) means. Week 8 was defined as the average of the Visit 8 and Visit 9 (Study Days 56 and 57) means. For missing Week 8 measurements, the mean from the last postbaseline visit in the treatment period was used.

Table LVGU.2 summarizes the change in mean cuff seated trough diastolic blood pressures for the full analysis population. The full analysis population was used for analyses of all efficacy variables. Of the 167 subjects in the full analysis population (55 placebo, 57 tadalafil 5 mg, and 55 tadalafil 20 mg), 161 were analyzed for the primary efficacy measure (53 placebo, 54 tadalafil 5 mg, and 54 tadalafil 20 mg). Six subjects in the full analysis population were excluded from the primary efficacy analysis because postbaseline measurements were not obtained. Reductions in mean diastolic blood pressure were observed in all 3 treatment groups at Week 8. Statistically significant reductions were observed in placebo-adjusted mean cuff seated trough diastolic blood pressures following once daily treatment with tadalafil 5 mg (-4.3 mm Hg; $p=.002$) and with tadalafil 20 mg (-5.3 mm Hg; $p<.001$).

Table LVGU.2. Change in Cuff Seated Trough Diastolic Blood Pressure, Full Analysis Population

Treatment	n	Mean (SD) Diastolic BP			Treatment Difference (SE)	95% CI	p-value (1-sided)
		Baseline	Endpoint ^a	Change from Baseline to Endpoint			
Placebo (N = 55)	53	98.2 (2.18)	95.1 (7.69)	-3.0 (7.24)	-	-	-
Tadalafil 5 mg (N = 57)	54	98.2 (2.38)	90.7 (8.46)	-7.5 (7.46)	-4.3 (1.43)	-7.2, -1.5	.002
Tadalafil 20 mg (N = 55)	54	97.9 (1.99)	89.6 (6.83)	-8.3 (6.38)	-5.3 (1.35)	-8.0, -2.7	<.001

Abbreviations: BP = blood pressure, CI = confidence interval, N = total number of subjects, n = subjects with nonmissing data at baseline and endpoint, SD = standard deviation, SE = standard error.

^a Endpoint is Week 8 or last nonmissing measurement.

Secondary Efficacy Measures

Changes in Cuff Seated Trough Systolic Blood Pressure from Baseline to Endpoint

Table LVGU.3 presents results for mean cuff seated trough systolic blood pressures for the full analysis population. Statistically significant reductions were observed for placebo-adjusted systolic blood pressures following once daily treatment with tadalafil 5 mg (-3.5 mm Hg; $p=.047$) and with tadalafil 20 mg (-3.6 mm Hg; $p=.047$).

Table LVGU.3. Change in Cuff Seated Trough Systolic Blood Pressure, Full Analysis Population

Treatment	n	Mean (SD) systolic BP (mm Hg)			Treatment Difference (SE)	95% CI	p-value (1-sided)
		Baseline	Endpoint ^a	Change from Baseline to Endpoint			
Placebo (N = 55)	53	147.4 (12.77)	145.3 (14.52)	-2.1 (10.85)	-	-	-
Tadalafil 5 mg (N = 57)	54	146.3 (13.25)	140.9 (15.14)	-5.5 (10.28)	-3.5 (2.06)	-7.6, 0.6	.047
Tadalafil 20 mg (N = 55)	54	149.4 (10.43)	143.9 (12.85)	-5.5 (10.72)	-3.6 (2.12)	-7.8, 0.6	.047

Abbreviations: BP = blood pressure, CI = confidence interval, N = total number of subjects, n = subjects with nonmissing data at baseline and endpoint, SD = standard deviation, SE = standard error.

^a Endpoint is Week 8 or last nonmissing measurement.

Changes in Ambulatory Diastolic Blood Pressure

Ambulatory blood pressure was measured every 15 minutes over a 24-hour interval at baseline and at the end of the 8-week treatment period. Changes in mean 24-hour ambulatory diastolic and systolic blood pressures were originally slated to be assessed for all subjects in the full analysis population. However, valid 24-hour ambulatory blood pressure data was obtained from only 66 subjects (18 placebo, 21 tadalafil 5 mg, and 27 tadalafil 20 mg). In many cases, data could not be obtained because subjects refused to wear the ambulatory blood pressure monitor (ABPM) device. In other cases, ABPM records were obtained but did not meet preselected criteria; as a result, those records were declared invalid.

Table LVGU.4 summarizes change in mean 24-hour ambulatory diastolic blood pressure from baseline to Week 8 for subjects in the full analysis population. Reductions in mean 24-hour ambulatory diastolic blood pressure were observed at Week 8 following once daily treatment with tadalafil 5 mg (-3.5 mm Hg) and tadalafil 20 mg (-4.8 mm Hg). There was little effect on diastolic blood pressure observed in the placebo group. Placebo-adjusted reductions in mean 24-hour ambulatory diastolic blood pressure were statistically significant for both tadalafil 5 mg (-3.8 mm Hg; $p=.003$) and tadalafil 20 mg (-4.7 mm Hg; $p=.001$).

Table LVGU.4. Change in 24-hour Mean for Ambulatory Diastolic Blood Pressure, Full Analysis Population

Treatment	n	Mean (SD) Diastolic BP (mm Hg)			Treatment Difference (SE)	95% CI	p-value (1-sided)
		Baseline	Week 8	Change from Baseline to Week 8			
Placebo (N = 55)	18	89.0 (7.55)	89.2 (8.77)	0.2 (3.13)	-	-	-
Tadalafil 5 mg (N = 57)	21	88.8 (8.94)	85.3 (9.07)	-3.5 (4.88)	-3.8 (1.32)	-6.5, -1.1.	.003
Tadalafil 20 mg (N = 55)	27	89.9 (7.93)	85.2 (8.79)	-4.8 (5.20)	-4.7 (1.44)	-7.6, -1.8	.001

Abbreviations: BP = blood pressure, CI= confidence interval, N = total number of subjects, n = subjects with nonmissing data at baseline and Week 8, SD = standard deviation, SE = standard error.

Changes in Ambulatory Systolic Blood Pressure

Table LVGU.5 summarizes changes in the mean 24-hour ambulatory systolic blood pressures for 66 subjects from the full analysis population. Reductions in mean 24-hour ambulatory systolic blood pressure were observed at Week 8 following once daily treatment with tadalafil 5 mg (-2.7 mm Hg) and tadalafil 20 mg (-5.7 mm Hg). There was little effect on systolic blood pressure observed in the placebo group. Placebo-adjusted reductions in mean 24-hour ambulatory systolic blood pressure were statistically significant for the tadalafil 20 mg group (-6.0 mm Hg; $p=.005$), but were not statistically significant for the tadalafil 5 mg group (-3.4 mm Hg; $p=.062$).

Table LVGU.5. Change in 24-hour Mean for Ambulatory Systolic Blood Pressure, Full Analysis Population

Treatment	n	Mean (SD) Systolic BP (mm Hg)			Treatment Difference (SE)	95% CI	p-value (1-sided)
		Baseline	Week 8	Change from Baseline to Week 8			
Placebo (N = 55)	18	142.1 (11.83)	142.6 (13.03)	0.5 (5.28)	-	-	-
Tadalafil 5 mg (N = 57)	21	139.2 (14.17)	136.5 (13.38)	-2.7 (7.09)	-3.4 (2.12)	-7.7, 1.0	.062
Tadalafil 20 mg (N = 55)	27	144.4 (13.00)	138.7 (12.33)	-5.7 (7.63)	-6.0 (2.19)	-10, -1.6	.005

Abbreviations: BP = blood pressure, CI = confidence interval, N = total number of subjects, n = subjects with nonmissing data at baseline and Week 8, SD = standard deviation, SE = standard error.

Trough-to-Peak Ratios of 24-Hour Ambulatory Diastolic and Systolic Blood Pressure

Table LVGU.6 presents trough-to-peak (T/P) ratios of the 24-hour ambulatory diastolic and systolic blood pressures at Week 8 for the full analysis population.

Table LVGU.6. Trough-to-Peak Ratio of 24-hour Ambulatory Diastolic and Systolic Blood Pressure at Week 8, Full Analysis Population

Treatment	n	Diastolic BP (mm Hg)				Systolic BP (mm Hg)			
		Mean (SD)			p-value	Mean (SD)			p-value
		T change	P change	T/P ratio		T change	P change	T/P ratio	
Placebo (N = 55)	18	-1.8 (7.23)	-8.3 (6.37)	0.3 (1.76)	-	-1.3 (8.31)	-9.3 (9.58)	-0.1 (2.85)	-
Tadalafil 5 mg (N = 57)	21	-2.3 (10.82)	-11.9 (6.25)	1.3 (4.56)	.681	-1.0 (13.07)	-12.6 (10.79)	0.1 (1.79)	.727
Tadalafil 20 mg (N = 55)	27	-5.9 (8.85)	-11.5 (10.58)	0.2 (2.58)	.637	-5.2 (10.17)	-14.8 (13.11)	1.9 (7.24)	.920

Abbreviations: BP = blood pressure, N = total number of subjects, n = subjects with nonmissing data at baseline and Week 8, T = trough, P = peak, SD = standard deviation.

Subjects Achieving Blood Pressure Control

Table LVGU.7 shows the number and percentage of subjects who achieved blood pressure control. Blood pressure control was defined as trough ambulatory (average of the hourly means at the 23rd and 24th hours postdose) or cuff seated systolic blood pressure <140 mm Hg and diastolic blood pressure <90 mm Hg after 8 weeks of treatment. Of those subjects evaluated for blood pressure control (subjects with nonmissing blood pressure data at Week 8), 9 placebo subjects (22.0%), 16 tadalafil 5 mg subjects (31.4%), and 16 tadalafil 20 mg subjects (32.7%) achieved cuff seated blood pressures <140/90 mm Hg at Week 8. Similar percentages were observed based on ambulatory blood pressure measurements: 4 placebo subjects (19.0%), 9 tadalafil 5 mg subjects (34.6%), and 11 tadalafil 20 mg subjects (34.4%) achieved ambulatory blood pressures <140/90 mm Hg at Week 8. The results for tadalafil treatment groups were not statistically significant compared with placebo.

Table LVGU.7. Subjects Achieving Blood Pressure Control at Week 8, Full Analysis Population

	Treatment											
	Placebo (N=55)			Tadalafil 5 mg (N=57)				Tadalafil 20 mg (N=55)				
	n	[1]	Count (%)	n	[1]	Count (%)	p-value	n	[1]	Count (%)	p-value	
Cuff Seated Blood Pressure												
SBP/DBP < 140/90 mm Hg	41		9 (22.0)	51		16 (31.4)	0.177	49		16 (32.7)	0.175	
DBP < 90 mm Hg	41		13 (31.7)	51		26 (51.0)		49		24 (49.0)		
SBP < 140 mm Hg	41		14 (34.1)	51		27 (52.9)		49		21 (42.9)		
Trough Ambulatory Blood Pressure												
SBP/DBP < 140/90 mm Hg	21		4 (19.0)	26		9 (34.6)	0.116	32		11 (34.4)	0.158	
DBP < 90 mm Hg	21		5 (23.8)	26		13 (50.0)		32		16 (50.0)		
SBP < 140 mm Hg	21		7 (33.3)	26		11 (42.3)		32		16 (50.0)		

Abbreviations: DBP = diastolic blood pressure, N = total number of subjects, n = subjects with nonmissing data at Week 8, SBP = systolic blood pressure.

Safety

Extent of Exposure

Table LVGU.8 summarizes the extent of exposure to study drug by treatment group for the safety population. The safety population was defined as subjects who were randomly assigned to treatment and received ≥ 1 dose of study drug during the double-blind treatment period. Subjects in the safety population were analyzed by the treatment actually received; in situations where a subject received mixed treatment during the double-blind treatment period, the subject was analyzed by the highest dose ever received. The safety population was used for the analysis of all safety variables. The mean duration of exposure was 48.9 days for placebo subjects, 52.4 days for tadalafil 5 mg subjects, and 56.1 days for tadalafil 20 mg subjects. The mean cumulative tadalafil dosage was 265.6 mg for subjects in the tadalafil 5 mg group and 1109.2 mg for subjects in the tadalafil 20 mg group.

Table LVGU.8. Extent of Exposure to Study Drug, Comparison of Treatment Groups (Treatment Period), Safety Population

	Treatment		
	Placebo (N = 61)	Tadalafil 5 mg (N = 62)	Tadalafil 20 mg (N = 57)
Duration of Exposure (days)			
n	58	60	53
Mean (SD)	48.9 (18.11)	52.4 (13.74)	56.1 (9.64)
Duration of Exposure (weeks), n (%)			
0 to <2	6 (9.8)	3 (4.8)	1 (1.8)
2 to <4	4 (6.6)	4 (6.5)	1 (1.8)
4 to <6	2 (3.3)	0	0
6 to <8	8 (13.1)	14 (22.6)	8 (14.0)
≥8	38 (62.3)	39 (62.9)	43 (75.4)
Cumulative Tadalafil Dosage^a (mg), n			
n	-	59	52
Mean (SD)	-	265.6 (66.07)	1109.2 (192.30)

Abbreviations: N = total number of subjects, n = subjects with nonmissing data at Week 8, SD = standard deviation.

^a Number of tadalafil doses taken x dosage (mg).

Overview of Adverse Events

Table LVGU.9 presents an overview of AEs reported during the study. A total of 86 subjects (47.8%) experienced treatment-emergent adverse events (TEAEs) in either the double-blind treatment period or the follow-up period. Of the total number of subjects who experienced TEAEs, 84 subjects experienced TEAEs during the double-blind treatment period, while 8 subjects experienced TEAEs during the 2-week follow-up period. Twenty-eight subjects experienced AEs during the double-blind treatment period or follow-up period that were considered by the investigator to be related to study drug. Additionally, 2 subjects experienced treatment-related AEs during the placebo lead-in period.

Table LVGU.9. Overview of Subject Incidence of Adverse Events, Safety Population

	Treatment			
	Placebo (N=61) n (%)	Tadalafil 5 mg (N=62) n (%)	Tadalafil 20 mg (N=57) n (%)	All Tadalafil (N=119) n (%)
Treatment Emergent Adverse Events	34 (55.7)	23 (37.1)	29 (50.9)	52 (43.7)
Double-Blind Treatment Period	34 (55.7)	21 (33.9)	29 (50.9)	50 (42.0)
Follow-up Period	1 (1.6)	6 (9.7)	1 (1.8)	7 (5.9)
Treatment Related Adverse Events	7 (11.5)	8 (12.9)	14 (24.6)	22 (18.5)
Placebo Lead-in Period	0	0	2 (3.5)	2 (1.7)
Double-Blind and Follow-up Period	7 (11.5)	8 (12.9)	13 (22.8)	21 (17.6)
Adverse Events Related to Study Procedures	3 (4.9)	5 (8.1)	3 (5.3)	8 (6.7)
Serious Adverse Events	0	0	0	0
Deaths	0	0	0	0
Adverse Events Leading to Discontinuation	6 (9.8)	4 (6.5)	3 (5.3)	7 (5.9)

Subjects are counted only once for each category.

Abbreviations: N = total number of subjects, n = number of subjects experiencing adverse events, SD = standard deviation.

Deaths

No deaths were reported during the study.

Serious Adverse Events

No serious adverse events (SAEs) were reported during the double-blind treatment period. One SAE (small intestinal obstruction) was reported during the placebo lead-in period; this subject did not meet the criteria for randomization and did not enter the double-blind treatment period.

Discontinuations

A total of 6 placebo subjects, 4 tadalafil 5 mg subjects, and 3 tadalafil 20 mg subjects experienced AEs leading to discontinuation. Five subjects discontinued due to treatment-related AEs: 2 placebo subjects (intermittent headaches and exacerbation of hypertension); and 3 tadalafil 20 mg subjects (dyspepsia, muscle spasms, and headache). Of the 13 subjects who discontinued due to AEs, 5 discontinued due to worsening or exacerbation of hypertension (3 placebo subjects and 2 tadalafil 5 mg subjects). One subject in the placebo group discontinued due to dizziness; this event was accompanied by fatigue and did not lead to syncope, was moderate in intensity, and was considered by the investigator to be unrelated to study drug or protocol procedures.

Treatment-Related Adverse Events

Overall, 28 subjects (15.6%) experienced AEs that were considered to be related to study drug: 7 subjects (11.5%) in the placebo group; 8 subjects (12.9%) in the tadalafil 5 mg group; and 13 subjects (22.8%) in the tadalafil 20 mg group. The most frequently reported treatment-related AEs included headache (5 placebo subjects, 5 tadalafil 20 mg subjects), dyspepsia (1 tadalafil 5 mg subject, 5 tadalafil 20 mg subjects), and myalgia (2 subjects each in the tadalafil 5 mg and 20 mg dose groups).

Study Procedures Related Adverse Events

Eleven subjects reported a total of 13 AEs that were considered to be related to study procedures. All of these AEs were mild or moderate in intensity. Six of the events occurred during the placebo lead-in period, while the other 7 occurred during the double-blind treatment period. Most of these events appeared to be caused by sphygmomanometer cuffs (such as rash or peripheral edema). One of the 13 AEs resulted in discontinuation: headache, reported by a subject (placebo group) during the double-blind treatment period.

Treatment-Emergent Adverse Events

Overall, 34 (55.7%) placebo subjects, 23 (37.1%) tadalafil 5 mg subjects, and 29 (50.9%) tadalafil 20 mg subjects experienced TEAEs during the treatment and follow-up periods. The TEAEs that were most frequently experienced by subjects included dyspepsia (2 tadalafil 5 mg subjects, 6 tadalafil 20 mg subjects), headache (5 placebo subjects, 7 tadalafil 20 mg subjects), nasopharyngitis (1 placebo subject, 4 tadalafil 5 mg subjects, 1 tadalafil 20 mg subject), nausea (1 placebo subject, 1 tadalafil 5 mg subject, 4 tadalafil 20 mg subjects), upper respiratory tract infection (2 placebo subjects, 3 tadalafil 5 mg subjects, 2 tadalafil 20 mg subjects), back pain (2 placebo subjects, 2 tadalafil 5 mg subjects, 2 tadalafil 20 mg subjects), and myalgia (2 tadalafil 5 mg subjects, 2 tadalafil 20 mg subjects).

Clinical Laboratory Evaluation

Standard laboratory tests, including serum chemistry, hematology, and urinalysis panels were performed. Blood samples for clinical laboratory analysis as well as urine samples were collected at Visit 1, Visit 4, Visit 6, and Visit 9 (follow-up period). No clinically meaningful changes were observed by the sponsor for hematology or serum chemistry values in this study.

Vital Signs

Vital signs (blood pressure, heart rate, respiratory rate, and temperature) were taken at each visit. No clinically meaningful changes were observed by the sponsor for vital signs in this study.

Electrocardiograms

A 12-lead electrocardiogram (ECG) was performed for each subject at Visit 1 and Visit 9 (follow-up period). No clinically meaningful changes were observed by the sponsor for ECG variables in this study.