Summary ID# 10303

Clinical Study Summary: Study H6D-MC-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

Date summary approved by Lilly: 05 August 2008

Title of Study: 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	
Investigator(s): 82 principal investigators.	
Study Center(s): 82 study centers throughout North America, Europe, and Japan.	
Publication(s) Based on the Study: None at this time.	
Length of Study: 2 years Date first subject enrolled: 18 August 2005 Date last subject completed: 16 August 2007	**Phase of Development:** 3

Objectives:

The primary objective of this study was to evaluate the safety and efficacy of the phosphodiesterase type 5 (PDE5) inhibitor tadalafil in the treatment of subjects with pulmonary arterial hypertension (PAH). A secondary objective was to evaluate tadalafil population pharmacokinetics (PK).

Safety was evaluated using adverse events (AEs), physical examinations, electrocardiograms (ECGs), and clinical laboratory data. Population PK was assessed by plasma tadalafil concentrations.

Efficacy was evaluated by the following endpoints:

Primary efficacy endpoint:

- 6-minute walk (6-MW) distance change from baseline to end of treatment (Week 16).

Secondary efficacy endpoints:

- World Health Organization (WHO) functional class change from baseline to end of treatment (Week 16).
- Time to first occurrence of clinical worsening, defined as any of the following: death, lung transplantation, atrial septostomy, hospitalization due to worsening PAH, initiation of new PAH therapy (for example, prostacyclin or analog, endothelin receptor antagonist, PDE5 inhibitor), or worsening of WHO functional class.
- Borg dyspnea score change from baseline to end of treatment (Week 16).
- In a subgroup of subjects, cardiopulmonary hemodynamic (includes heart rate, mean pulmonary artery pressure [mPAP], pulmonary vascular resistance [PVR], mean right atrial pressure [mRAP], cardiac index [CI], cardiac output [CO], pulmonary capillary wedge pressure [PCWP], mean arterial pressure [mAP], mixed venous oxygen saturation [MVO2], systemic arterial oxygen saturation[SaO2], and systemic vascular resistance [SVR]) changes from baseline to Week 16.
- Quality of Life (QoL), as measured by Short-Form-36v2 (SF-36) Health Survey and European Quality of Life (EuroQoL) Questionnaire scores from baseline to end of treatment (Week 16). The SF-36 had each domain scored by summing the individual items and transforming the scores into a 0 to 100 scale, with higher scores indicating better health status or functioning. The EuroQoL index score was a value between -1 and 1; the higher the score, the better the QoL.

Study Design: This was a Phase 3, 18-week, multicenter, randomized, double-blind, placebo-controlled study of the PDE5 inhibitor tadalafil given orally to subjects with PAH. Subjects were to be equally randomized to groups receiving 1 of 5 treatments (tadalafil 2.5, 10, 20, 40 mg, or placebo) once daily for 16 weeks. Selected subjects were eligible to enter an extension trial after the 16-week treatment period; subjects not entering the extension trial had a follow-up safety visit at Week 18 (2 weeks after study treatment discontinuation).

Number of subjects:

Planned: 400 subjects; 80 subjects per treatment group
Randomized: 406 subjects; 82 placebo, 324 tadalafil
Randomized and Treated: 405 subjects; 82 placebo, 323 tadalafil
Completed 16-Week Treatment: 341 subjects; 69 placebo, 272 tadalafil

Diagnosis and Main Criteria for Inclusion: Subjects were at least 12 years of age and had a diagnosis of PAH that was idiopathic, related to collagen disease, related to anorexigen use, related to human immunodeficiency virus (HIV) infection, associated with an atrial septal defect, or associated with surgical repair of at least 1 year in duration of a congenital systemic-to-pulmonary shunt (for example, ventricular septal defect, patent ductus arteriosus). The diagnosis was established by a resting mPAP ≥25 mm Hg, pulmonary wedge pressure ≤15 mm Hg, and PVR ≥3 Wood units via right heart catheterization.

Test Product, Dose, and Mode of Administration: Tadalafil 2.5, 10, 20, or 40 mg once daily, to be taken orally.

Duration of Treatment: 16 weeks

Reference Therapy, Dose, and Mode of Administration: Placebo once daily to be taken orally.

Outcomes (Variables):

Efficacy: The primary efficacy outcome was the 6-MW test. Secondary efficacy outcomes included: WHO functional class, time to clinical worsening, Borg dyspnea score, and hemodynamic measurements.

Safety: Safety was evaluated using treatment-emergent adverse events (TEAEs), physical examinations (including vital signs), and clinical laboratory data.

Pharmacokinetic/Pharmacodynamic: Population PK was assessed by plasma tadalafil concentrations.

Health Outcomes: Quality-of-life assessments were assessed via the SF-36 Health Survey and EuroQoL Questionnaire.

Evaluation Methods:

Statistical: Analysis of efficacy endpoints was performed on the intent-to-treat (ITT) population (that is, randomized and used study medication) by randomized treatment.

The primary efficacy endpoint was the change from baseline to end of treatment (Week 16) in 6-MW distance (the distance a subject could walk in 6 minutes). The null hypothesis of no difference between each of the tadalafil treatment groups and placebo was tested using a permutation-based procedure similar to the Mann-Whitney test stratified by PAH etiology, bosentan use, and baseline 6-MW distance (≤325 and >325 meters). In the analysis, the change from baseline values were ranked without regard to stratum (including only subjects for placebo and the active treatment arm being tested in the pairwise comparison) using the observed change from baseline to Week 16. Subjects who died or discontinued due to PAH worsening were assigned the lowest rank. For subjects who discontinued due to treatment-related AEs, no change from baseline was assumed to assign the rank. The last observation carried forward (LOCF) for missing Week 16 data was used for subjects with missing change from baseline to Week 16.

Step-down testing began with the tadalafil 40-mg dose and then proceeded downward based upon achieving a significance level of 0.01 for the preceding dose. Descriptive analyses (that is, point estimates and confidence intervals) adopted an observed data approach, as well as the LOCF approach, and were conducted for the change from baseline in 6-MW distance. If statistical significance was achieved for the primary endpoint, the secondary endpoints were evaluated using the step-down testing procedure beginning with the tadalafil 40-mg dose and proceeding downward based upon achieving a significance level of 0.05 for the preceding dose and test (WHO functional class, time to clinical worsening, and Borg dyspnea score – in that progression).

Six-MW distance and Borg dyspnea score were tested using a non-parametric permutation test on ranks stratified by PAH etiology (idiopathic/anorexigen use and other), bosentan use (yes/no), and baseline 6-MW distance (≤325 and >325 meters). Ranks were assigned to reduce bias introduced by any data missing due to changes in disease status. Change in WHO functional class for subjects who improved, had no change, or worsened from baseline was tested using the Cochran-Mantel-Haenszel (CMH) test and controlled stratification factors (PAH etiology, bosentan use, and baseline 6-MW distance). Missing values were considered as worsened in the analysis. Time from randomization to first occurrence of clinical worsening was analyzed using a non-parametric permutation test on the log-rank score and controlled stratification factors. Kaplan-Meier estimates of time to clinical worsening were also done. For the analysis of cardiopulmonary hemodynamic parameters, each treatment group was compared with baseline using a paired *t* test. For analyses of QoL questionnaires, each tadalafil treatment group was compared with placebo using an analysis of covariance (ANCOVA) model with effects for treatment, all stratification factors, and the corresponding baseline as a covariate.

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Evaluation Methods (Concluded):
Safety was summarized descriptively.

A sample size of 400 subjects (80 subjects per treatment group) was planned to provide approximately 90% power at an α-level (two-sided) of 0.001 to detect a 45-meter placebo-adjusted treatment effect in 6-MW distance (change from baseline to Week 16).

PK/Pharmacodynamics: The plasma concentration versus time data together with dosing information and prespecified patient factors of clinical and demographic interest were pooled and analyzed using population techniques to characterize tadalafil PK following once-daily administration of tadalafil 2.5, 10, 20, and 40 mg.

Summary:
Demographics:
Of the ITT population in Study LVGY, 323 subjects were randomly assigned to tadalafil (2.5 mg: 82, 10 mg: 80, 20 mg: 82, or 40 mg: 79) and 82 subjects were randomly assigned to placebo. The mean age of all subjects was 54 years, with the majority of subjects being Caucasian (80.5%) and female (78.3%). Pulmonary arterial hypertension etiologies were predominantly idiopathic (61.0%) and related to collagen vascular disease (23.5%). Slightly more than half (53.3%) of subjects in Study LVGY were receiving concomitant bosentan therapy. Mean duration of prior bosentan therapy in Study LVGY ranged from 1.6 to 2.0 years. While all WHO functional classes were represented in Study LVGY, the majority of subjects were either WHO Functional Class III (65.2%) or II (32.1%). The mean baseline 6-MW distance was 343.6 meters.

Efficacy Results:
Primary Endpoint:
The tadalafil 40 mg treatment group had statistically significant improvements in 6-MW distance compared to placebo after 16 weeks of treatment (p=0.0004). The tadalafil 40 mg treatment group had a placebo-adjusted treatment difference of 32.8 meters (95% confidence interval: 15.2 to 50.3 meters).

Treatment with tadalafil 20 mg did not meet the prespecified statistical significance level at 0.01 (p=0.0278). The placebo-adjusted treatment difference for tadalafil 20 mg was 27.5 meters (95% confidence interval: 10.6 to 44.3 meters).

Secondary Endpoints:
Since tadalafil 20 mg did not meet the prespecified statistical significance level at 0.01 (p=0.0278) only tadalafil 40 mg was evaluated for statistical significance in secondary outcomes as per the step-down analysis. In the secondary protocol-specified step-down analyses there were no statistically significant differences between subjects receiving tadalafil 40 mg compared to placebo in incidences of WHO functional class improvement, no change, or worsening. Since there were no statistically significant treatment differences from placebo in WHO functional class, the descriptive statistics and inferential tests on other secondary variables (time to clinical worsening and Borg dyspnea score) were presented as additional information only.

The raw p-value of time to clinical worsening in the tadalafil 40 mg treatment group compared to placebo was 0.041. The probability of subjects not having a clinical worsening event at Week 16 was 94% for the tadalafil 40 mg treatment group (95% confidence interval: 85% to 98%) compared to 84% for placebo group (95% confidence interval: 74% to 90%).

Mean (standard deviation [SD]) change from baseline of Borg dyspnea score (subject-perceived level of dyspnea at end of treatment after the 6-MW test) was -0.7 (1.8) for tadalafil 40 mg and 0.4 (1.9) for placebo.

The tadalafil 40 mg treatment group had statistically significant changes from baseline in some cardiopulmonary hemodynamic parameters (mPAP, PVR, CI, and CO [$p<0.05$]) but not in others (heart rate, mRAP, PCWP, mAP, MVO2, SaO2, and SVR).

Changes in SF-36 were seen in almost all 8 domains of QoL in tadalafil treatment groups compared to placebo with tadalafil 40 mg having statistically significant changes in 6 domains ($p<0.05$). Statistically significant changes in EuroQoL were also seen in all tadalafil treatment groups compared to placebo in the index score (both United States and United Kingdom; $p<0.05$). Only the tadalafil 40 mg treatment group achieved a statistically significant change compared to placebo in the current health state visual analog scale (VAS; $p=0.0215$).

Due to a decrease in bioavailability with tadalafil 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 tadalafil exposure. 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 tadalafil 40 mg with concomitant bosentan therapy as compared to those receiving tadalafil 40 mg alone.

Safety Results:
Table LVGY.1 presents AEs occurring in 3% of PBO subjects or 3% of combined tadalafil subjects. The majority of subjects (>79%) experienced at least 1 TEAE during the study's treatment period (Table LVGY.1). The incidence of all AEs was lowest in the placebo treatment group (79.3%) and highest in the tadalafil 40 mg treatment group (94.9%).

The most common TEAEs (>7.5%) across all tadalafil treatment groups were headache, diarrhea, nausea, back pain, dizziness, dyspepsia, peripheral edema, and pulmonary hypertension. The most common TEAEs (>7.5%) in females across all tadalafil treatment groups were headache, diarrhea, nausea, back pain, dizziness, flushing, myalgia, and nasopharyngitis. The most common TEAEs (≥3 subjects) in males across all tadalafil treatment groups were peripheral edema, headache, dyspepsia, dyspnea, pulmonary hypertension, and pain in extremity.

Fifty-four subjects (placebo: n=12, tadalafil 2.5 mg: n=14, tadalafil 10 mg: n=10, tadalafil 20 mg: n=11, and tadalafil 40 mg: n=7) had serious adverse events (SAEs; Table LVGY.2). Incidences of subjects who experienced at least 1 SAE were similar to placebo and across all tadalafil groups. Serious adverse events that occurred in more than 1 subject in any tadalafil treatment group were pulmonary hypertension, right ventricular failure, and anemia.

Thirteen subjects (placebo: n=5, tadalafil 2.5 mg: n=4, tadalafil 10 mg: n=1, tadalafil 20 mg: n=1, and tadalafil 40 mg: n=2) discontinued due to nonfatal SAEs (Table LVGY.3). Incidences of subjects who experienced at least 1 AE that led to discontinuation from the study during the treatment period were similar to placebo and across all tadalafil treatment groups. Adverse events that led to subject discontinuation during the study's treatment period in more than 1 subject in any tadalafil treatment group were pulmonary hypertension, dyspnea, back pain, and right ventricular failure. The nonfatal SAEs in the tadalafil treatment groups that led to subject discontinuations were pulmonary hypertension, diabetes mellitus inadequate control, right ventricular failure, menorrhagia, cardiac failure, and drug hypersensitivity.

Three subjects died due to SAEs of pulmonary hypertension (placebo), sudden death (tadalafil 10 mg), and histiocytosis haematophagic syndrome (tadalafil 20 mg).

There were minimal group mean changes and minimal differences across any of the treatment groups in hematology, coagulation, urinalysis, and serum chemistry panel parameters. The incidence of an elevated international normalized ratio (INR) was also consistent across all treatment groups. There were few numbers of subjects having abnormal shift changes by visit or by most extreme value at anytime in hematology, coagulation, urinalysis, and serum chemistry panel parameters during the study.

Table LVGY.1. Summary of Treatment-Emergent Adverse Events Occurring in at Least 3.0% of Placebo- or Combined Tadalafil-Treated Subjects by Preferred Term in Descending Order of Incidence in the Combined Tadalafil Group
All Intent-to-Treat Subjects (N=405)

	Placebo (N=82)		T2.5mg (N=82)		T10mg (N=80)		T20mg (N=82)		T40mg (N=79)		All tadalafil (N=323)	
Preferred Term	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients with >= 1 TEAE	65	(79.3)	72	(87.8)	72	(90.0)	69	(84.1)	75	(94.9)	288	(89.2)
Headache	12	(14.6)	15	(18.3)	30	(37.5)	26	(31.7)	33	(41.8)	104	(32.2)
Diarrhoea	8	(9.8)	9	(11.0)	9	(11.3)	6	(7.3)	9	(11.4)	33	(10.2)
Nausea	5	(6.1)	6	(7.3)	7	(8.8)	8	(9.8)	9	(11.4)	30	(9.3)
Back pain	5	(6.1)	5	(6.1)	5	(6.3)	10	(12.2)	8	(10.1)	28	(8.7)
Dizziness	7	(8.5)	9	(11.0)	8	(10.0)	5	(6.1)	6	(7.6)	28	(8.7)
Dyspepsia	2	(2.4)	4	(4.9)	2	(2.5)	11	(13.4)	8	(10.1)	25	(7.7)
Oedema peripheral	7	(8.5)	7	(8.5)	6	(7.5)	7	(8.5)	5	(6.3)	25	(7.7)
Pulmonary hypertension	7	(8.5)	7	(8.5)	5	(6.3)	7	(8.5)	6	(7.6)	25	(7.7)
Flushing	2	(2.4)	3	(3.7)	5	(6.3)	5	(6.1)	10	(12.7)	23	(7.1)
Myalgia	3	(3.7)	2	(2.4)	3	(3.8)	7	(8.5)	11	(13.9)	23	(7.1)
Nasopharyngitis	6	(7.3)	4	(4.9)	6	(7.5)	2	(2.4)	10	(12.7)	22	(6.8)
Dyspnoea	3	(3.7)	8	(9.8)	4	(5.0)	4	(4.9)	5	(6.3)	21	(6.5)
Pain in extremity	2	(2.4)	3	(3.7)	4	(5.0)	4	(4.9)	9	(11.4)	20	(6.2)
Muscle spasms	2	(2.4)	4	(4.9)	8	(10.0)	5	(6.1)	2	(2.5)	19	(5.9)
Upper respiratory tract infection	3	(3.7)	5	(6.1)	5	(6.3)	4	(4.9)	5	(6.3)	19	(5.9)
Epistaxis	3	(3.7)	6	(7.3)	4	(5.0)	5	(6.1)	3	(3.8)	18	(5.6)
Cough	7	(8.5)	2	(2.4)	6	(7.5)	2	(2.4)	7	(8.9)	17	(5.3)
Palpitations	2	(2.4)	5	(6.1)	7	(8.8)	3	(3.7)	1	(1.3)	16	(5.0)
Arthralgia	1	(1.2)	4	(4.9)	7	(8.8)	2	(2.4)	2	(2.5)	15	(4.6)
Chest pain	1	(1.2)	4	(4.9)	1	(1.3)	5	(6.1)	5	(6.3)	15	(4.6)
Vomiting	1	(1.2)	2	(2.4)	2	(2.5)	6	(7.3)	5	(6.3)	15	(4.6)

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Table LVGY.1. Summary of Treatment-Emergent Adverse Events Occurring in at Least 3.0% of Placebo- or Combined Tadalafil-Treated Subjects by Preferred Term in Descending Order of Incidence in the Combined Tadalafil Group
All Intent-to-Treat Subjects (N=405) (Concluded)

	Placebo (N=82)		T2.5mg (N=82)		T10mg (N=80)		T20mg (N=82)		T40mg (N=79)		All tadalafil (N=323)	
Preferred Term	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Fatigue	3	(3.7)	4	(4.9)	1	(1.3)	4	(4.9)	5	(6.3)	14	(4.3)
Nasal congestion	1	(1.2)	3	(3.7)	3	(3.8)	0	(0.0)	7	(8.9)	13	(4.0)
Oedema	1	(1.2)	3	(3.7)	1	(1.3)	4	(4.9)	4	(5.1)	12	(3.7)
Bronchitis	0	(0.0)	3	(3.7)	3	(3.8)	1	(1.2)	4	(5.1)	11	(3.4)
Hot flush	2	(2.4)	4	(4.9)	2	(2.5)	2	(2.4)	3	(3.8)	11	(3.4)
Rash	3	(3.7)	1	(1.2)	1	(1.3)	5	(6.1)	4	(5.1)	11	(3.4)
Insomnia	2	(2.4)	2	(2.4)	1	(1.3)	4	(4.9)	3	(3.8)	10	(3.1)
Urinary tract infection	0	(0.0)	3	(3.7)	2	(2.5)	2	(2.4)	3	(3.8)	10	(3.1)
Vision blurred	1	(1.2)	2	(2.4)	2	(2.5)	4	(4.9)	2	(2.5)	10	(3.1)
Gastrooesophageal reflux disease	3	(3.7)	1	(1.2)	3	(3.8)	1	(1.2)	4	(5.1)	9	(2.8)
Chest discomfort	3	(3.7)	2	(2.4)	1	(1.3)	3	(3.7)	2	(2.5)	8	(2.5)
Influenza	3	(3.7)	2	(2.4)	2	(2.5)	1	(1.2)	2	(2.5)	7	(2.2)
Gastroenteritis viral	3	(3.7)	0	(0.0)	1	(1.3)	4	(4.9)	0	(0.0)	5	(1.5)
Cardiac failure	3	(3.7)	1	(1.2)	1	(1.3)	1	(1.2)	1	(1.3)	4	(1.2)
Conjunctival haemorrhage	3	(3.7)	1	(1.2)	0	(0.0)	2	(2.4)	1	(1.3)	4	(1.2)
Weight increased	3	(3.7)	1	(1.2)	1	(1.3)	1	(1.2)	0	(0.0)	3	(0.9)
Eye pain	3	(3.7)	0	(0.0)	1	(1.3)	1	(1.2)	0	(0.0)	2	(0.6)

Abbreviations: N = number of randomized subjects who received study medication; n = number of subjects with at least one TEAE; TEAE = treatment-emergent adverse event.

* Subjects may be counted in than one category.

Source: AEFN03GY

Table LVGY.2. Summary of Serious Adverse Events by Preferred Term in Descending Order of Incidence in the Combined Tadalafil Group
Summary by Randomized Study Treatment Group
All ITT Subjects (N=405)
Study H6D-MC-LVGY

Preferred Term	Placebo (N=82) n	(%)	T2.5mg (N=82) n	(%)	T10mg (N=80) n	(%)	T20mg (N=82) n	(%)	T40mg (N=79) n	(%)	All tadalafil (N=323) n	(%)
Patients with >= 1 Serious AE	12	(14.6)	14	(17.1)	10	(12.5)	11	(13.4)	7	(8.9)	42	(13.0)
Pulmonary hypertension	1	(1.2)	4	(4.9)	3	(3.8)	0	(0.0)	2	(2.5)	9	(2.8)
Right ventricular failure	1	(1.2)	2	(2.4)	2	(2.5)	1	(1.2)	0	(0.0)	5	(1.5)
Anaemia	0	(0.0)	2	(2.4)	0	(0.0)	1	(1.2)	0	(0.0)	3	(0.9)
Dyspnoea	0	(0.0)	1	(1.2)	1	(1.3)	1	(1.2)	0	(0.0)	3	(0.9)
Upper respiratory tract infection	0	(0.0)	1	(1.2)	0	(0.0)	1	(1.2)	0	(0.0)	2	(0.6)
Atrial flutter	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.3)	1	(0.3)
Bronchitis	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)
Bronchospasm	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)
Cardiac failure	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.3)	1	(0.3)
Chest pain	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	1	(0.3)
Dehydration	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	1	(0.3)
Diabetes mellitus inadequate control	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)
Drug hypersensitivity	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.3)	1	(0.3)
Gastritis	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	1	(0.3)
Gastroenteritis	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	1	(0.3)
Gastroenteritis viral	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	1	(0.3)
Haematocrit decreased	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)
Haemoglobin decreased	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)
Headache	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.3)	1	(0.3)
Histiocytosis haematophagic	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	1	(0.3)
Hypoaesthesia	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)

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Table LVGY.2. Summary of Serious Adverse Events by Preferred Term in Descending Order of Incidence in the Combined Tadalafil Group
Summary by Randomized Study Treatment Group
All ITT Subjects (N=405)
Study H6D-MC-LVGY (Continued)

	Placebo (N=82)		T2.5mg (N=82)		T10mg (N=80)		T20mg (N=82)		T40mg (N=79)		All tadalafil (N=323)	
Preferred Term	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Hypokalaemia	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	1	(0.3)
Hypotension	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	1	(0.3)
Influenza like illness	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)
Menorrhagia	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	1	(0.3)
Mental status changes	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)
Non-cardiac chest pain	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.3)	1	(0.3)
Oesophageal varices haemorrhage	0	(0.0)	0	(0.0)	1	(1.3)	0	(0.0)	0	(0.0)	1	(0.3)
Pain	0	(0.0)	0	(0.0)	1	(1.3)	0	(0.0)	0	(0.0)	1	(0.3)
Pericarditis	0	(0.0)	0	(0.0)	1	(1.3)	0	(0.0)	0	(0.0)	1	(0.3)
Pleural effusion	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)
Pneumonia	2	(2.4)	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	1	(0.3)
Pneumothorax	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)
Priapism	0	(0.0)	0	(0.0)	1	(1.3)	0	(0.0)	0	(0.0)	1	(0.3)
Pulmonary embolism	1	(1.2)	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	1	(0.3)
Respiratory distress	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	1	(0.3)
Scleroderma	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	1	(0.3)
Sudden death	0	(0.0)	0	(0.0)	1	(1.3)	0	(0.0)	0	(0.0)	1	(0.3)
Swelling face	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.3)	1	(0.3)
Urinary tract infection	0	(0.0)	0	(0.0)	1	(1.3)	0	(0.0)	0	(0.0)	1	(0.3)
Vasculitis	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)
Weight increased	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)
Acute prerenal failure	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Diarrhoea	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

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Table LVGY.2. Summary of Serious Adverse Events by Preferred Term in Descending Order of Incidence in the Combined Tadalafil Group
Summary by Randomized Study Treatment Group
All ITT Subjects (N=405)
Study H6D-MC-LVGY (Concluded)

	Placebo (N=82)		T2.5mg (N=82)		T10mg (N=80)		T20mg (N=82)		T40mg (N=79)		All tadalafil (N=323)	
Preferred Term	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
General physical health deterioration	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Hyponatraemia	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Nausea	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Oedema peripheral	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Retinal artery occlusion	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Vomiting	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

Abbreviations: N = number of randomized subjects who received study medication; n = number of subjects with at least one serious AE.

* Subjects may be counted in than one category.

MedDRA Version 10.0
Program Location: RMP.H6DSLVGY.SASPGM(AEFN19GY)
Output Location: RMP.H6DO.LVGY(AEFN19GY)
Data Set Location: RMP.SAS.H6DS.L.MCLVGY.ADS

Table LVGY.3. Summary of Adverse Events Leading to Discontinuations by Preferred Term in Descending Order of Incidence in the Combined Tadalafil Group
Summary by Randomized Study Treatment Group
All ITT Subjects (N=405)
Study H6D-MC-LVGY Adverse Events (Preferred Term) Leading to Discontinuation
Incidence by Decreasing Frequency within the Tadalafil Treatment Group
All ITT Subjects

	Placebo (N=82)		2.5mg (N=82)		10mg (N=80)		20mg (N=82)		40mg (N=79)		All tadalafil (N=323)	
Preferred Term	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients with >= 1 AE leading to discontinuation	13	(15.9)	13	(15.9)	7	(8.8)	9	(11.0)	7	(8.9)	36	(11.1)
Pulmonary hypertension	7	(8.5)	4	(4.9)	2	(2.5)	4	(4.9)	3	(3.8)	13	(4.0)
Back pain	0	(0.0)	0	(0.0)	1	(1.3)	0	(0.0)	1	(1.3)	2	(0.6)
Dyspnoea	1	(1.2)	2	(2.4)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.6)
Right ventricular failure	0	(0.0)	1	(1.2)	1	(1.3)	0	(0.0)	0	(0.0)	2	(0.6)
Abdominal pain upper	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	1	(0.3)
Cardiac failure	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.3)	1	(0.3)
Cardiac failure acute	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)
Dermatitis allergic	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	1	(0.3)
Diabetes mellitus inadequate control	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)
Drug hypersensitivity	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.3)	1	(0.3)
Headache	0	(0.0)	0	(0.0)	1	(1.3)	0	(0.0)	0	(0.0)	1	(0.3)
Hepatic congestion	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)
Histiocytosis haematophagic	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	1	(0.3)
Influenza like illness	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)
Menorrhagia	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	1	(0.3)
Neutropenia	0	(0.0)	0	(0.0)	1	(1.3)	0	(0.0)	0	(0.0)	1	(0.3)
Pain	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.3)	1	(0.3)
Palpitations	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)
Skin ulcer	0	(0.0)	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)

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Table LVGY.3. Summary of Adverse Events Leading to Discontinuations by Preferred Term in Descending Order of Incidence in the Combined Tadalafil Group
Summary by Randomized Study Treatment Group
All ITT Subjects (N=405)
Study H6D-MC-LVGY Adverse Events (Preferred Term) Leading to Discontinuation
Incidence by Decreasing Frequency within the Tadalafil Treatment Group
All ITT Subjects (Concluded)

	Placebo (N=82)		2.5mg (N=82)		10mg (N=80)		20mg (N=82)		40mg (N=79)		All tadalafil (N=323)	
Preferred Term	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Sudden death	0	(0.0)	0	(0.0)	1	(1.3)	0	(0.0)	0	(0.0)	1	(0.3)
Syncope	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	0	(0.0)	1	(0.3)
General physical health deterioration	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pulmonary embolism	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Retinal artery occlusion	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Vomiting	1	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

Abbreviations: N = number of randomized subjects who received study medication; n = number of subjects with an adverse event leading to discontinuation.

* Includes events that were considered possibly related to study treatment as judged by the investigator.

MedDRA Version 10.0
Program Location: RMP.H6DSLVGY.SASPGM(AEFN28GY)
Output Location: RMP.H6DO.LVGY(AEFN28GY)
Data Set Location: RMP.SAS.H6DS.L.MCLVGY.ADS