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APPLICATION NUMBER:

22-332

MEDICAL REVIEW(S)

CLINICAL AND STATISTICAL REVIEW

Application Type	NDA
Submission Number	22,332
Submission Code	6 S
Letter Date	July 23, 2008
Stamp Date	July 24, 2008
PDUFA Goal Date	May 24, 2009
Reviewers' Names	Maryann Gordon, M.D. (Medical) Valeria Freidlin, PhD. (Statistics)
Review Completion Date	March 5, 2009
Established Name	tadalafil
(Proposed) Trade Name	Adcirca™
Therapeutic Class	phosphodiesterase 5 inhibitor
Applicant	Eli Lilly and Company
Priority Designation:	S
Formulation	tablets
Dosing Regimen	once daily
Indication	treatment of pulmonary arterial hypertension (PAH)
Intended Population	PAH, WHO group 1

1 Executive Summary

1.1 Recommendation on Regulatory Action

The primary medical and statistical reviewers of the new drug application (NDA) 22,332 involving the use of tadalafil in the treatment of patients with pulmonary arterial hypertension (PAH) are recommending approval.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

None

1.2.2 Required Phase 4 Commitments

None

1.2.3 Other Phase 4 Requests

The sponsor should be encouraged to evaluate higher doses of tadalafil in patients with PAH. The 40 mg once daily dose was the highest dose tested in this population and it was shown to be an effective dose in improving exercise tolerance only. The 20 mg once daily dose was marginally effective; doses lower than 20 mg had effects similar to placebo. There are no obvious dose-limiting serious adverse events.

Interaction study with ambrisentan is recommended.

1.3 Summary of Clinical Findings

Pulmonary arterial hypertension (PAH) is a chronic and progressive disease characterized by elevation of pulmonary artery pressure and pulmonary vascular resistance (PVR), leading to right heart failure and death. The most common etiology is idiopathic. Other etiologies include PAH in association with collagen vascular diseases, human immunodeficiency virus infection, congenital systemic-to-pulmonary shunts, and use of anorexigens.

Phosphodiesterase type 5 (PDE5) is the major phosphodiesterase in the pulmonary vasculature. The inhibition of this enzyme is thought to result in high cGMP levels which could, in turn, contribute to antiproliferative effects. Sildenafil, for example, is such an inhibitor. It is approved for increasing exercise tolerance in patients with PAH (Revatio®) as well as for the treatment of erectile dysfunction (Viagra®). Tadalafil, also an inhibitor of the PDE5 enzyme, is approved for the treatment of erectile dysfunction (Cialis®).

1.3.1 Brief Overview of Clinical Program

The safety and efficacy of tadalafil in patients with PAH has been demonstrated in one prospective, randomized, double-blind, placebo-controlled study (H6D-MC-LVGY)¹. Subjects in that study included those at least 12 years of age and with a diagnosis of PAH that was either (a) idiopathic, (b) related to collagen vascular disease, (c) related to anorexigen use, (d) related to HIV infection, (e) associated with an atrial septal defect, or (f) with surgical repair (of at least 1-year duration) of a congenital systemic-to-pulmonary shunt (e.g., ventricular septal defect, patent ductus arteriosus). The subjects had to have established at time of diagnosis a resting mean pulmonary artery pressure ≥ 25 mm Hg, pulmonary artery wedge pressure ≤ 15 mm Hg, and pulmonary vascular resistance ≥ 3 Wood units via right heart catheterization. Their baseline 6-minute walk test distance had to be between 150 and 450 meters, inclusive, at screening and they had to have World Health Organization (WHO) functional class I, II, III or IV status.

In addition to the one efficacy study, there were five clinical pharmacology studies in healthy subjects (three drug interaction studies, one food effect study, and one PK in Japanese subjects) and one long term open label, uncontrolled extension study (H6D-MC-LVGX) in patients.

1.3.2 Efficacy

In the evaluation of its efficacy in PAH, tadalafil 40 mg once daily, compared to placebo, was shown to significantly increase mean walking distance. The placebo subtracted treatment effect for subjects randomized to tadalafil 40 mg was 32.8 meters (95% confidence interval: 15.2 to 50.3 meters, $p < 0.001$). This effect on exercise is similar to those seen with many other PAH treatments approved for increasing exercise tolerance. Doses of tadalafil other than 40 mg were not found to be significantly² better than placebo in prolonging walk distance.

Secondary endpoints including change in WHO functional class, time to clinical worsening, and change in Borg scale tended to show numerical but not statistically significant improvement with the 40 mg dose compared to placebo.

Those subjects in the tadalafil 40 mg group who were not taking bosentan had a treatment effect twice as large as those taking bosentan.

¹ A single study was deemed to be sufficient to demonstrate efficacy in PAH population (letter to sponsor dated 6-23-05).

² The significance level for this study was 0.01 (2-sided) since it was the only one used to support efficacy.

In a subgroup of subjects with cardiopulmonary hemodynamic evaluation, the tadalafil 40 mg treatment group had improvements from baseline in mean pulmonary artery pressure, pulmonary vascular resistance, cardiac index, and cardiac output similar to the placebo group.

1.3.3 Safety

Tadalafil was first approved in Australia on October 15, 2002 for the treatment of ED. Since then, tadalafil has been approved for ED in 114 countries and is marketed in approximately 105 countries. As of September 30, 2007, approximately — patients worldwide have been exposed to tadalafil. The sponsor submitted reports from regulatory authorities and spontaneously reported adverse events in patients receiving tadalafil for pulmonary hypertension that have been reported to Lilly as off-label use with commercially available product.

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Adverse events reported by subjects with PAH were similar to those reported by subjects with ED.

Adverse events most commonly reported by the tadalafil 40 mg group in the placebo controlled study LVGY included headache, myalgia, flushing, and nasopharyngitis (placebo subtracted incidence rates were 27%, 10%, 11%, and 6%, respectively).

Deaths

There were three deaths in study LVGY (placebo: worsening PAH, tadalafil 10 mg: sudden death, tadalafil 20 mg: hematophagic histiocytosis related to lupus). Association with either sudden death or death resulting from hematophagic histiocytosis with tadalafil use appears to be unlikely.

At the time of the interim data lock, there were 11 deaths reported during the long term uncontrolled extension study LVGX. Deaths were attributed to right ventricular failure, sudden cardiac death, lung cancer, cardiac arrest, myocardial infarction, pneumonia, and sudden death. A causative link between any of these deaths and tadalafil use seems unlikely.

Serious adverse events

The serious adverse events reported by at least 2 tadalafil subjects in study LVGY included pulmonary hypertension (9), right ventricular failure (5), anemia (3), dyspnea (3), and upper respiratory tract infection (2). Adverse events leading to study drug discontinuation included right ventricular failure, pulmonary hypertension, back pain, and dyspnea. These events are not unexpected in this patient population.

Serious safety reported by at least three subjects in the uncontrolled extension study LVGX included pulmonary hypertension (9), right ventricular failure (9), chest pain³ (8), pneumonia (6), anemia (3), and peripheral edema.

³ Includes chest and non cardiac chest pain

There was, however, increased reporting of menorrhagia and/or vaginal haemorrhage in the tadalafil group (8)⁴ compared to placebo (0).

1.3.4 Dosing Regimen and Administration

Dosing of tadalafil in the efficacy study ranged from 2.5 mg to 40 mg once daily. Only the 40 mg dose group showed convincing evidence of effectiveness. There was no evidence of dose-related serious adverse events. Currently, there is no rationale for approving doses other than 40 mg for the PAH indication with the exception of lower starting dose (20 mg) for patients with mild to moderate hepatic or renal impairment.

1.3.5 Drug-Drug Interactions

Concomitant treatment with bosentan, a moderate inducer of CYP3A, reduced steady-state tadalafil AUC by 41.5% and C_{max} by 26.6% in healthy volunteers. This decrease in tadalafil AUC when used with bosentan was also observed in the population analysis of PAH subjects.

The pharmacokinetics of digoxin, a P-gp substrate, were not affected when tadalafil was co-administered (in healthy volunteers).

Study LVHM demonstrated that administration with an oral contraceptive with single and multiple doses of 40 mg tadalafil resulted in higher AUC (54% and 26%, respectively) and C_{max} (90% and 70%, respectively) of ethinylestradiol. The effect of tadalafil on levonorgestrel pharmacokinetics following single and multiple dose oral contraceptive administration was negligible.

1.3.6 Special Populations

The previous pharmacokinetic data reported in special populations and reflected in current Cialis® labeling⁵ (approved doses up to 20 mg) may be applied to 40 mg administration, with the addition of those provided below.

The individual tadalafil plasma concentration time profiles for females and males are essentially similar following single and multiple, once-daily doses of 40 mg tadalafil. The population pharmacokinetic analysis of subjects with PAH indicated that systemic exposure to tadalafil was not influenced by gender. There is no indication of a pharmacokinetic basis for specific dose adjustments based upon gender.

⁴ Only one subject (909 8551) reported menorrhagia as a serious adverse event and was discontinued for this event.

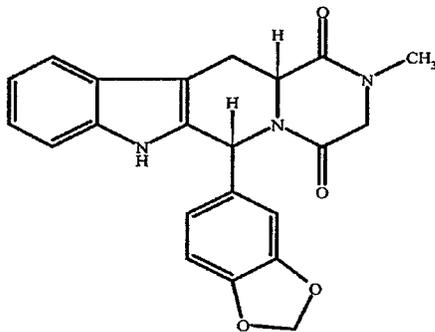
⁵ Dosage adjustments for patients with mild or moderate hepatic impairment and patients with moderate or severe renal insufficiency.

Population-based assessment of any influence of ethnicity on tadalafil disposition was based on stratification by white and non-white subjects with PAH; no influence of ethnicity on tadalafil CL/F was identified. There are no apparent pharmacokinetic differences necessitating dose adjustment based upon ethnic origin.

2 Introduction and background

2.1 Product information

Tadalafil (ADCIRCA™) is a phosphodiesterase type 5 (PDE5) inhibitor. It has the empirical formula $C_{22}H_{19}N_3O_4$ representing a molecular weight of 389.41. The structural formula is:



The chemical designation is pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)-. It is a crystalline solid that is practically insoluble in water and very slightly soluble in ethanol.

Tadalafil is available as orange, film-coated, almond-shaped tablets for oral administration. Each tablet contains 20 mg of tadalafil and the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, hypromellose, iron oxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate, talc, titanium dioxide, and triacetin.

Tadalafil is indicated for the treatment of pulmonary arterial hypertension to improve exercise capacity. The recommended dose is 40 mg once daily. The pharmacokinetics, safety or effectiveness of tadalafil in pediatric patients has not been established.

2.2 Currently available treatments for indication

If approved, tadalafil would be the seventh drug currently approved for the treatment of PAH. The other six drugs include epoprostenol, treprostinil, and iloprost (prostacyclins), sildenafil (a phosphodiesterase type 5 inhibitor), bosentan and ambrisentan (endothelin receptor antagonist).

2.3 Availability of Proposed Active Ingredient in the United States

As of October 15, 2007, tadalafil (CIALIS®) is approved for the treatment of erectile dysfunction in 114 countries and marketed in approximately 105 countries. Tadalafil may be taken on demand (5, 10, and 20 mg) or once daily (2.5 and 5 mg).

As of September 30, 2007, approximately _____ patients worldwide have been exposed to tadalafil. Approximately 18,400 patients have been exposed to tadalafil in completed clinical efficacy and safety studies, including studies of PAH.

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2.4 Important Issues With Pharmacologically Related Products

Sildenafil (Revatio®), a phosphodiesterase type 5 inhibitor similar to tadalafil, was approved for use as a treatment for PAH in the U.S. in 2005. The following are safety concerns with this type of product.

- Sildenafil is contraindicated in patients with regular and/or intermittent use of organic nitrates.
- There have been reports of sudden loss of vision in one or both eyes while taking a PDE5 inhibitor including sildenafil. Such an event may be a sign of non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision.
- There have been reports of sudden decrease or loss of hearing while taking a PDE5 inhibitor, including sildenafil.

2.5 Presubmission Regulatory Activity

Guidance meetings between Lilly and the Division of Cardiovascular and Renal Products were conducted to discuss the development of tadalafil for treatment of PAH on April 19, 2005, May 26, 2006, and January 15, 2008. The meetings resulted in agreement a) on the clinical pharmacology package and b) that a single study (LVGY) was an acceptable approach to support approval of tadalafil for the treatment of PAH at a p-value of (2-sided) for the primary endpoint. No additional non-clinical studies were requested.

Other notable actions include the following:

- July 20, 2006, FDA granted an Orphan Drug Designation for the use of tadalafil in the treatment of PAH.
- November 16, 2006, FDA issued a Written Request for the conduct of clinical trials in pediatric patients with PAH.

2.6 Other Relevant Background Information

NA

3 Significant Findings from other Review Disciplines

3.1 CMC

3.2 Animal Pharmacology/Toxicology

4 Data Sources, Review Strategy, and Data Integrity

4.1 Sources of Clinical Data

The electronic submission is located in the EDR:

Application Type/Number: nda022332

Incoming Document Type: E

Incoming Document Type Sequence Number: 001

Letter Date: 07/23/2008

4.2 Table of Clinical Studies

The studies submitted in support of NDA #22,332 are listed below.

Table 5.2.2. Tabular Listing of Clinical Studies (Continued)

Study Id Status; Report Type	Objective(s)	Enrollment Start and End # Planned # Entered # Completed	Design; Control Type	Test and Control Drug(s); Dose, Route, Regimen	HS or P; # Completed (M/F); Entered (M/F); Mean Age Years (Range)	Diagnosis or Inclusion Criteria	Treatment Duration	Primary Endpoint(s)
H6D-MC-LVGZ Complete; ClinPharm	PK & Safety	Jul-Sep05 Enter: 15 (all received ≥1 dose TAD) Complete: 13	Open-label, randomized, 3-period crossover	Test: QD, PO, TAD 2 x 20 mg tab or BID Bosentan 1 x 125 mg alone and in combination w/ washout ≥7days between tx	HS; Complete: 13 (13M/0F) Enter: 15 (13M/0F) Age: 29 (19-52)	HS; M Age: 18-65, inclusive	3 separate 10-day tx w/7 day washout between tx	PK parameters bosentan used w/ & w/out multiple TAD 40-mg doses
H6D-EW- LVHM Complete; ClinPharm	PK & Safety	Jan-Aug07 Enter: 30 Complete: 26	Double-blind, 3-period, 2-sequence, randomized, crossover, PLA-control	Test: QD, PO, TAD 2 x 20 mg tab concom w/oral contraceptive or PLA concom w/oral contraceptive	HS; Complete: 26 (0M/26F) Enter: 30 (0M/30F) Age: 27 (21-43)	Overtly HS; F premen on oral contraceptive Age: 21-45, inclusive	12 weeks	PK parameters of multiple TAD 40-mg dose concom used w/oral contraceptive or oral contraceptive alone
H6D-EW-LVHL Complete; ClinPharm	PK & Safety	Dec06-Mar07 Enter: 20 Complete: 19	Open-label, single- sequence	Test: Dig 0.25 mg BID on Day 1 then 0.25 mg QD x next 16 days QD, PO, TAD 2 x 20 mg tab concom w/Dig x final 10 days of Dig	HS; Complete: 19 (13M/6F) Enter: 20 (14M/6F) Age: 40 (18-57)	HS; M or F (non- childbearing) Age: 18-60	17 days	PK parameters of Dig w/ & w/out multiple TAD 40-mg dose

(continued)

Table 5.2.2. Tabular Listing of Clinical Studies

Study Id Status; Report Type	Objective(s)	Enrollment Start and End # Planned # Entered # Completed	Design; Control Type	Test and Control Drug(s); Dose, Route, Regimen	HS or P; # Completed (M/F); Entered (M/F); Mean Age Years (Range)	Diagnosis or Inclusion Criteria	Treatment Duration	Primary Endpoint(s)
H6D-EW-LV10 Complete; ClinPharm	Food Effect	Jan-Feb07 Enter: 15 Complete: 12	Open-label, randomized, 2-period crossover	Test: PO, single-dose TAD 2 x 20 mg tab fasted w/in 30 min of starting FDA-defined HF breakfast	HS; Complete: 13 (7M/6F) fed 14 (9M/5F) fast Enter: 15 (9M/6F) Age: 38 (19-61)	HS; M & F Age: 18-65	Single-dose TAD x 2 tx w/27 days between doses	PK parameters at 40-mg dose under fed & fasted states
H6D-MC-LVHC Complete; ClinPharm	Safety & PK in Japanese M & F subjects	Jul-Aug 06 Enter: 24 Dose >= 1 x TAD: 18 PLA: 6 Complete: 21 (TAD 15, PLA 6)	Randomized, Double-blind, P1A-control	Test: QD, PO, TAD 2 x 20 mg tab or PLA	HS; Complete: 21 (12M/9F) Enter: 24 (13M/11F) Age: TAD 22 (20-29) PLA 21(20-23)	HS; M & F (Japanese) Age: 20-45 BMI: ≥18 & <25 kg/m2	10 days	Safety & PK parameters at multiple 40-mg dose

(continued)

Table 5.2.2. Tabular Listing of Clinical Studies (Continued)

Study Id Status; Report Type	Objective(s)	Enrollment Start and End # Planned # Entered # Completed	Design; Control Type	Test and Control Drug(s); Dose, Route, Regimen	HS or P; # Completed (M/F); Entered (M/F); Mean Age Years (Range)	Diagnosis or Inclusion Criteria	Treatment Duration	Primary Endpoint(s)
H6D-MC-LVGY Complete (PopPK/PD); ClinPharm	PopPK	See below (LVGY)	See below (LVGY)	See below (LVGY)	See below (LVGY)	See below (LVGY)	See below (LVGY)	Characterize TAD PK & develop model to describe time-course, if any, of 6-MW response, and its relationship to TAD exposure and other covariates
H6D-MC-LVGY Complete Full CSR	Efficacy & Safety	Aug05-Aug07 Plan: 400 Complete: 341	Randomized, double-blind, P1A-control	Test (PO QD) tab (4): TAD 1 x 2.5 mg & 3 x PLA or TAD 1 x 10 mg & 3 x PLA or TAD 1 x 20 mg & 3 x PLA or TAD 2 x 20 mg & 2 x PLA PLA (PO QD) tab (4) 4 x PLA	P; Complete: 341 Enter: (received drug): 405 (88M/317F) Age: 54 (15-90)	P w/PAH; Age: ≥12 years	16 weeks	6-MW distance change from baseline to Week 16

(continued)

Table 5.2.2. Tabular Listing of Clinical Studies (Concluded)

Study Id Status: Repeat Type	Objective(s)	Enrollment Start and End # Planned # Entered # Completed	Design: Control Type	Test and Control Drug(s): Dose, Route, Regimen	H/S or P: # Completed (MF); Entered (MF); Mean Age Years (Range)	Diagnosis or Inclusion Criteria	Treatment Duration	Primary Endpoint(s)
H6D-MC-LVGX (Extension of LVGY interim dataset) Ongoing: aCSR	Safety & Efficacy	08Dec05 ongoing Data cutoff: 04Oct07 Plus (Interim) (Part 1): 2100 Enter: Total: 357 Complete (Part 1): 125	Part 1: Double-blind Part 2: Open-label	Test (Part 1): (PO QD) tab (2) TAD 1 x 20 mg & 1 x PLA or TAD 2 x 20 mg Test (Part 2): (PO QD) tab (2) TAD 2 x 20 mg	Complete Part 1: 125 Included in analysis and entered Part 1: 357 (79M/278F) Age: 54 (15-90)	P w/PAH: who are eligible to enter extension trial: *P de'd PLA-control (LVGY) for clinical worsening & was on PLA, TAD 2.5, 10, or 20 mg; or *P completed Week 16 PLA-control (LVGY)	Part 1: 52 weeks Part 2: tx until TAD commercial available for tx of PAH or until Lilly concludes study	Part 1: Safety parameters Part 2: Safety parameters

4.3 Review Strategy

This review is a joint clinical-statistical review. The focus of this review is primarily the results of the double blind, randomized, placebo controlled efficacy study H6D-MC-LVGX.

The safety information was derived from the studies listed in 4.2 as well as post marketing reports for the ED indication.

4.4 Data Quality and Integrity

A routine DSI inspection was requested for study H6D-MC-LVGX. The site inspected was found to have adhered to the applicable regulations and good clinical practices governing the conduct of clinical investigations. There were minor protocol violations but DSI concluded that “the study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.”

4.5 Compliance with Good Clinical Practices

Each protocol used to support this new indication stated that the study was to be conducted in compliance with Good Clinical Practices. With the exception of minor protocol violations, there is no indication that good clinical practices were not followed by any investigator.

4.6 Financial Disclosures

A sponsor representative signed FDA Form 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators).

There is a single completed Form FDA 3455 (Disclosure: Financial Interests and Arrangements of Clinical Investigators) signed by the sponsor representative that outlines the equity interest of the investigator.

Information for some of the investigators (mostly sub investigators) was incomplete. Both forms are included in the electronic NDA submission.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

5.2 Pharmacodynamics

5.3 Exposure-Response Relationship

6 INTEGRATED REVIEW OF EFFICACY

The efficacy of tadalafil was established, with the agreement of the Division, with the results of one randomized, placebo controlled, parallel group clinical trial (provided the study met certain stringent conditions).

6.1 Indication

The proposed indication is the treatment of PAH to improve exercise capacity.

6.1.1 Methods

Study H6D-MC-LVGY was entitled: 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. This multicenter study was conducted by 82 investigators, all cardiology or physicians of pulmonary or collagen diseases, at 82 study sites. Sites were located in Europe (Belgium, France, Germany, Ireland, Italy, Spain, U.K.) North America (U.S.A, Canada), Asia (Japan). Of the total number of subjects randomized, 48% were from the U.S.A. This study was reviewed in its entirety and site #111 was selected as the site to be audited by DSI. The findings of DSI declare that the "study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication."

6.1.2 General Discussion of Endpoints

The primary endpoint was the 6-minute walk (6-MW) distance change from baseline at the end of treatment (week 16). Subjects who dropped from the study prematurely had their last data point carried forward. Walk distance has been the endpoint of interest for most of the approved drugs used to treat PAH.

Secondary endpoints for the study included:

- 1) improvement in WHO functional class,
- 2) time to clinical worsening defined as any of the following:
 - death,
 - lung transplantation,
 - atrial septostomy,
 - hospitalization because of worsening PAH,
 - initiation of new PAH therapy (prostacyclin or analog, endothelin receptor antagonist, PDE5 inhibitor), or
 - worsening WHO functional class (using stratified permutation based log-rank test), and
- 3) change in Borg dyspnea score (using the same procedure as the primary endpoint).

These are well accepted secondary endpoints.

Significance testing was to follow the above order and be performed at a 0.05 (2-sided) level of significance.

Additional endpoints (and, generally, of minor interest):

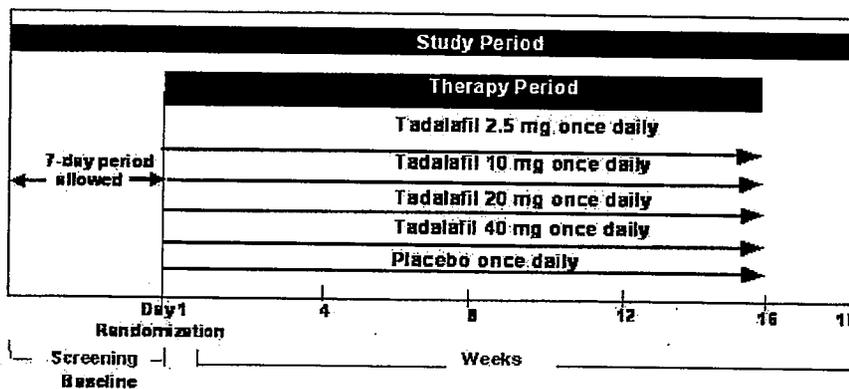
- Cardiopulmonary hemodynamic (includes mean pulmonary artery pressure, pulmonary vascular resistance, mean right atrial pressure, cardiac index, cardiac output, pulmonary capillary wedge pressure, mean arterial pressure, mixed venous oxygen saturation, systemic arterial oxygen saturation, systemic vascular resistance) changes from baseline to Week 16.
- Quality of Life, as measured by change in Short-Form-36v2 Health Survey (SF-36v2) and EuroQol scores from baseline to Week 16.

6.1.3 Study Design

This was a multicenter, randomized, double-blind, parallel-group, placebo-controlled double-dummy study. Subjects who met all eligibility criteria were stratified by PAH etiology, bosentan use, and baseline 6-minute walk distance (≤ 325 m and > 325 m). Subjects were then randomized⁶ 1:1:1:1 to receive either tadalafil 2.5 mg, 10 mg, 20 mg, 40 mg, or placebo orally once daily for 16 weeks. Those subjects completing

⁶ The randomization scheme was performed by a computerized interactive voice-response system (IVRS) at a central location for all sites. The IVRS system was used to balance the number of subjects receiving right heart catheterization for each treatment arm.

the Week 16 visit were allowed to be considered for the extension trial. Those subjects not going into the extension trial had an additional study visit 2 weeks later (Week 18 visit).



The walk test at Week 12 was used to determine if peak walk distances (12 hours after last drug intake) were substantially different from trough walk distances (24 hours after last drug intake). Subjects were instructed to take their study drug after the 6 minute walk test and blood sample collection. The previous dose should have been taken the day before the study visit.

There were six amendments to the protocol (original dated April 5, 2005):

- Amendment 1 was administrative and released prior to subject enrollment to the study.
- Amendment 2 was a result of changes requested by a medical expert in PAH and included adding an upper limit of systolic and diastolic blood pressures at screening in addition to other minor clarifications. Amendment 2 was released prior to any subject enrollment.
- Amendment 3 added the EuroQoL Questionnaire for capture of QoL measures in the study. Amendment 3 was released prior to any subject enrollment.
- Amendment 4 was initiated because the FDA requested that ophthalmologic exams be required. In addition, the number of study sites planned was increased to 80 (from 60).
- Amendment 5 a) amended the inclusion/exclusion criteria to include subjects with PAH related to HIV infection, b) expanded inclusion criterion for established diagnosis of PAH to include left ventricular end diastolic pressure for subjects in which pulmonary artery wedge pressure was unobtainable during right heart catheterization, c) changed inclusion criterion regarding the daily maintenance dose for subjects receiving bosentan therapy d) changed exclusion criterion for symptomatic coronary artery disease to specify disease that occurred within 5 years of study entry.

-Amendment 6 encompassed all changes to the protocol required to allow study sites in Japan to participate in the study. The number of sites planned was increased to 90 (from 80) in order to accommodate the addition of study sites in Japan.

These changes are minor and would not be expected to have a substantial impact on the outcome of the study.

6.1.4 Efficacy Findings (combined Clinical and Statistical Review)

6.1.4.1 Baseline Characteristics and Subject Disposition

There were 457 subjects entered into the study from Western Europe, North America, Japan, and UK. North America enrolled the majority of subjects (60%). Of the total entered, there were 406 randomized to a treatment group and 405 who received at least one dose of study drug. The number of subjects randomized per treatment group ranged from 79 to 82.

Type of Subject

The study subjects were approximately 54 years of age, predominantly female and predominantly white. The percentage of subjects at least 75 years of age was greatest for placebo (13%) compared to tadalafil groups (range 6%-9%). Mean weight was around 75 kgs.

Most subjects had PAH less than 4 years. The etiology of PAH was classified as idiopathic for the majority of the subjects; those with PAH "related to collagen vascular disease" had the second most common etiology. More than half of subjects were taking bosentan, the mean 6-minute walk distance ranged from 343 to 352 m, and most were WHO functional class II or III. Common concomitant medications (reported by at least 50 tadalafil subjects) included bosentan, acetylsalicylic acid, furosemide, levothyroxine, oxygen, paracetamol, potassium, and spironolactone.

Overall, the treatment groups were reasonably well balanced.

Subject disposition

The table below shows the outcome for all 406 subjects.

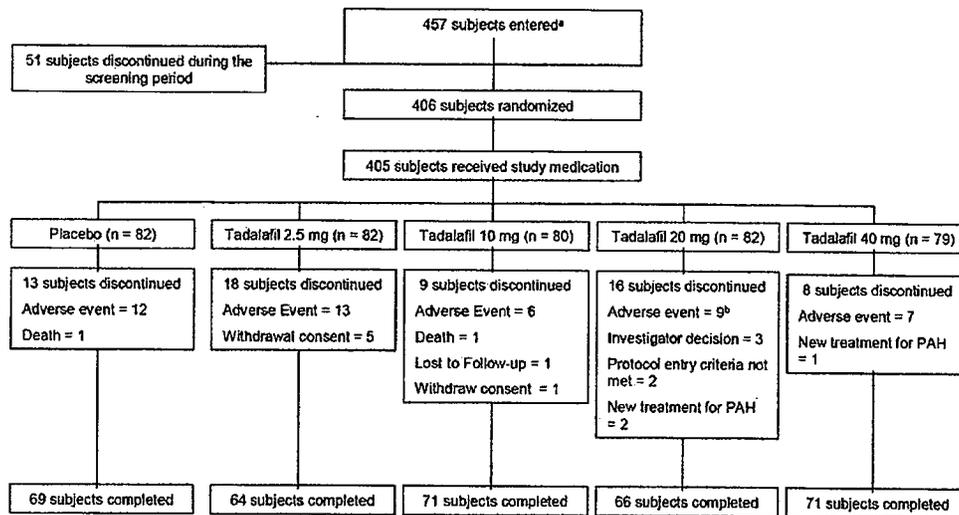
Number and (%) of subjects

	tadalafil				
	Placebo	2.5 mg	10 mg	20 mg	40 mg
randomized	82	82	80	82	79
completed week 16	69 (84)	64 (78)	71 (89)	66 (80)	71 (90)
early dc'd	13 (16)	18 (22)	9 (11)	16 (20)	8 (10)
died	1 (1)	0	1 (1)	0	0
dc'd for adverse event	12 (15)	13 (16)	6 (8)	9 (11)	7 (9)
dc'd because of invest decision	0	0	0	3	0
Lost to follow up	0	0	1 (1)	0	0
dc'd because of protocol not met	0	0	0	2 (2)	0
dc'd because of needing other PAH meds	0	0	0	2 (2)	1 (1)
withdrew consent	0	5 (6)	1 (1)	0	0

The tadalafil 40 mg group had a somewhat higher percentage (90%) completing the entire study (16 weeks) compared to the other groups. The tadalafil 2.5 mg group had the lowest percentage of completers (78%). The placebo completion rate was 84%.

The majority of premature drop outs were reported to have occurred because of adverse event(s). The placebo group had the greatest percentage of drop outs for this reason (15%) and tadalafil 10 mg had the lowest (8%) followed by tadalafil 40 mg (9%). The tadalafil 2.5 mg group had the highest rate of "withdrew consent" (6%).

Subject disposition is shown in the figure below.



^a Subjects were allowed to screen more than once but were only counted as entered into the study once.

^b One tadalafil 20-mg treated subject (912-8701) discontinued the study due to an adverse event and then later died due to the adverse event. The death was considered to have occurred during the study.

Source: [RMP.H6DO.LVGY(RTFN01GY)].

6.1.4.2 Primary endpoint

The primary efficacy endpoint was the 6 min walk test at week 16.

The total number of subjects excluded from the primary endpoint analysis was 13 (3 placebo, 3 tadalafil 2.5 mg, 2 tadalafil 10 mg, 2 tadalafil 20 mg, and 3 tadalafil 40 mg). The results of the walk test are shown below.

6 Min walk (m) at week 16

	Placebo n=79	Tadalafil			
		2.5 mg n=79	10 mg n=78	20 mg n=80	40 mg n=76
Mean baseline walk distance (SD)	347.49 (81.18)	346.53 (71.60)	340.01 (72.80)	338.26 (74.45)	352.67 (78.75)
Mean change from baseline at week 16 (SD)	9.21 (59.96)	21.79 (60.83)	28.6 (62.17)	36.23 (47.53)	41.14 (49.39)
95% CI	-4.22, 22.65	8.17, 35.42	14.58, 42.61	25.65, 46.81	29.85, 52.42
Placebo subtracted means*	-	10	16	22	26
P value+	-	0.402	0.0466	0.0278	0.0004

^95% CI is calculated based on t distribution.

+Permutation test stratified by PAH etiology, bosentan use, and baseline 6 min walk distance (≤ 325 m and >325 m) on rank compared to placebo.

*Hodges-Lehmann method.

Statistical Methods

The ITT population for the primary analysis included all subjects who were randomized to treatment and received at least 1 dose of study drug. 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 testing level of significance for the primary and secondary endpoints was 2-sided 0.01 and 2-sided 0.05, respectively. A step-down procedure, starting with tadalafil 40 mg group, was used to address the multiplicity issues when comparing each tadalafil dose with placebo on multiple endpoints. The endpoints were tested in this order: change in 6-MW distance (primary), change in WHO functional class, time to first occurrence of clinical worsening, and change in Borg dyspnea score. A 2-dimensional multiplicity adjustment algorithm began testing from tadalafil 40 mg compared with placebo on the primary endpoint. If this was statistically significant at the 2-sided level of significance at 0.01 then, (i) testing proceeded downward to the next lower dose on the primary endpoint tested at the 2-sided level of significance at 0.01, and (ii) testing proceeded to the next secondary endpoint tested at the 2-sided level of significant at 0.05.

Reviewer's comment: as the secondary endpoints are only to support the primary endpoint and not for additional indications, then it seems reasonable to use the 0.05 significance level for the study-wise type I error for the secondary endpoints, and the multiplicity adjustment procedure also seems reasonable, though it does not ensure a strong control of study-wise type I error rate.

The null hypothesis of no difference between each of the tadalafil treatment groups and placebo was tested. Primary and key secondary analyses based on continuous

outcomes (that is, 6-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 as follows:

– For subjects who died or discontinued from the study due to clinical worsening (lung transplantation, atrial septostomy, worsening of WHO functional class, hospitalization due to worsening of PAH, or initiation of new PAH therapy), ranks were assigned as if the subject had the lowest possible outcome.

–For subjects who discontinued early due to treatment-related AEs in the absence of clinical worsening, a value of zero was imputed for the change from baseline in 6-MW distance (that is, no benefit from treatment) and ranked relative to the remainder of the data.

–For all other subjects, including those who completed the Week 16 visit but the visit was outside of the visit window or who discontinued early for any other reason, the most recent nonmissing postbaseline data were carried forward (last observation carried forward; LOCF).

Descriptive statistics were also calculated. Subjects who died or discontinued due to disease worsening had their data treated as missing in later scheduled visits with last available nonmissing value imputed (LOCF). Post hoc sensitivity analysis for the calculation of descriptive statistics was also done to mimic the ranking strategy in the primary analysis.

Since randomization was stratified by 3 factors (PAH etiology, use of bosentan, baseline 6-MW distance), the treatment difference compared to placebo was estimated using analysis of covariance (ANCOVA) with Type II sum of squares. This was considered more appropriate than the population mean. The ANCOVA model included effects for treatment group, centered baseline of 6-MW distance, PAH etiology, and bosentan use. Normality of the residuals was also tested. Additionally, the treatment difference compared to placebo and the corresponding 95% confidence intervals were estimated by Hodges-Lehmann method.

Only the 40 mg dose was significantly better than placebo ($p=0.0004$) in prolonging the walk distance at week 16. Tadalafil 20 mg could be weakly supported as the minimum effective dose, although it did not meet the prespecified significance level of 0.01 ($p=0.028$).

Doses above 40 mg should be examined in future studies.

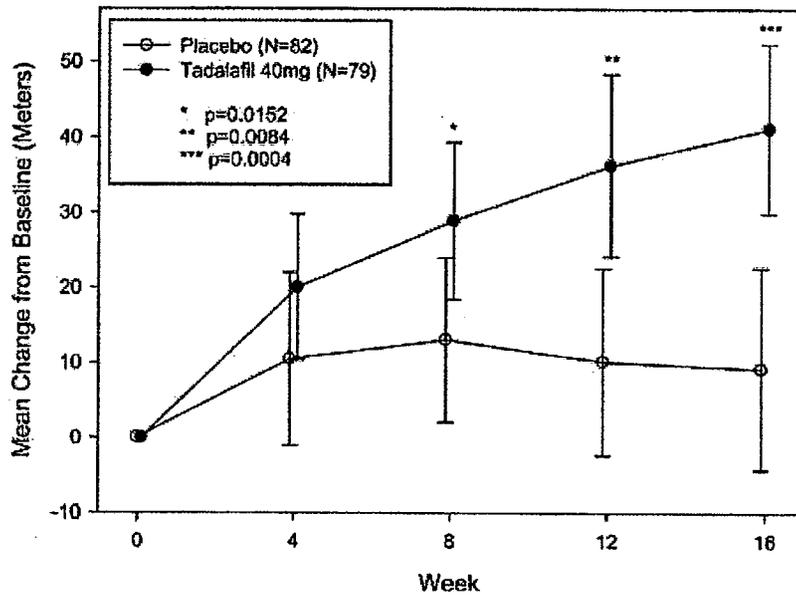
Exercise testing at other visits

The 6 minute walk tests were performed at weeks 4, 8, and 12 as well as at week 16. The testing at week 12 was conducted at the “trough drug concentration”. The results for all weeks are shown below only for placebo and tadalafil 40 mg.

	Placebo n=79	tadalafil 40 mg n=76
Mean baseline walk distance (SD)	347.49 (81.18)	352.67(78.75)
# of subjects evaluated at week 4	79	72
Mean change from baseline at week 4 (SD)	10.47 (51.44)	20.03 (41.36)
Treatment effect	-	10
# of subjects evaluated at week 8	79	76
Mean change from baseline at week 8 (SD)	13.04 (48.79)	28.91 (45.74)
Treatment effect	-	16
# of subjects evaluated at week 12	79	76
Mean change from baseline at week 12 (SD)	10.14 (55.49)	36.25 (53.00)
Treatment effect	-	26
# of subjects evaluated at week 16	79	76
Mean change from baseline at week 16 (SD)	9.21 (59.96)	41.14 (49.39)
Treatment effect	-	32

At week 12, the walk test was performed at trough drug concentration. The results for the tadalafil 40 mg dose showed a placebo subtracted 26 m improvement over baseline. This improvement in walk distance was the same as that obtained at week 16 (peak). From this information, one can conclude that once a day dosing is adequate.

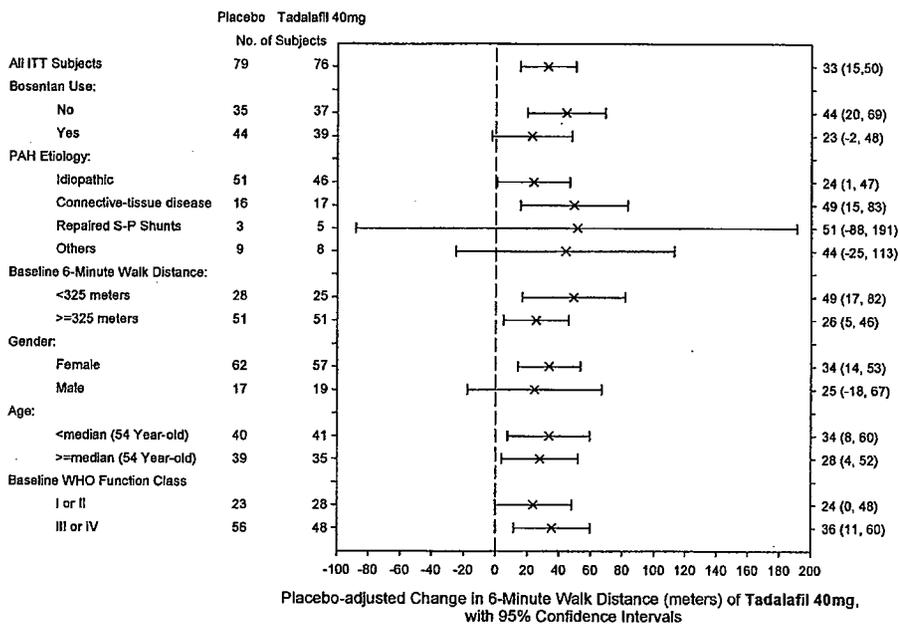
At every visit, the tadalafil subjects improved their walk distance. The figure below shows the walk distance at the different visits for placebo and tadalafil 40 mg groups.



Subgroups

The subgroups of particular interest include bosentan use, age, gender, baseline walk distance, and etiology of PAH (idiopathic, connective-tissue disease, repaired congenital systemic-to-pulmonary shunt, others), and baseline WHO functional class (combined Class I and II, combined Class III and IV). Few nonwhite subjects were studied so racial differences in efficacy were not examined.

The placebo subtracted changes in 6 minute walk test for the different subgroups are shown below for the tadalafil 40 mg group only.



Repaired S-P Shunts=Repaired Congenital systemic-to-pulmonary shunt.

Bosentan use

A total of 216 subjects (53%) were taking concomitant bosentan. (Subjects were stratified at the time of randomization according to whether or not they were taking bosentan.)

Baseline characteristics of the placebo and tadalafil groups, with and without concomitant bosentan, revealed that compared to subjects not on bosentan, the subjects taking bosentan were a little younger and more likely to have had their PAH longer than 4 years. Baseline walk distance was somewhat longer for the subjects on bosentan.

The results of the 6 minute walk test, grouped by bosentan use, are shown below for the placebo and tadalafil 40 mg subjects.

6 min walk: Mean change from baseline at week 16 (m)

placebo		Tad 40 mg	
yes+	no^	yes+	no^
n=44	n=35	n=39	n=37
18.0	-6.0	40.7	38.4
Trx effect (Ancova method)		22.7#	44.3***

+Taking concomitant bosentan

^not taking bosentan

#p= 0.076 for bosentan plus placebo compared to bosentan plus tadalafil.

***p=0.0006 for placebo compared to tadalafil.

Those subjects in the tadalafil 40 mg group who were not taking bosentan had a treatment effect twice as large as those taking bosentan.

Age

The placebo subtracted walk distances mean change from baseline at week 16 were similar for those less than 54 years and those greater than 54 years.

Gender

There were 3.5 times as many females enrolled in the study as males. The increases in the treatment effect were roughly similar for the females and the males.

Baseline walk test

The subjects were grouped according to baseline 6 min walk distance (≤ 325 m versus > 325 m). In the tadalafil 40 mg group, those subjects who walked less at baseline had a 20 m greater increase in walk distance at endpoint compared to those who walked longer at baseline.

Etiology of disease

Subjects were stratified by PAH etiology (idiopathic/anorexigen use (n=263) and other (n=142)) at randomization. The subjects in the stratum "idiopathic/anorexigen use" and randomized to tadalafil 40 mg had a mean placebo subtracted increase of 23 m at endpoint. This compares to the 51 m placebo subtracted gain by the other stratum.

The other large etiology group (collagen vascular disease) had a placebo subtracted increase in 6 minute walk distances of 14 m.

Baseline WHO functional class

A total of 134 subjects were classified as WHO functional classes I (n=4) and II (n=130) at baseline. At endpoint, the tadalafil 40 mg treatment group had a placebo subtracted mean increase of 27 m over baseline.

A total of 271 subjects were classified as WHO Functional Class III (n= 264) and IV (n=9). The placebo subtracted mean increase in walk distance was 35 m change from baseline at endpoint for the tadalafil 40 mg group.

Secondary Endpoints

Following the step-down procedure, statistical analysis of the secondary endpoints can be only evaluated for tadalafil 40 mg, since only tadalafil 40 mg had a statistically significant improvement on the primary endpoint. All secondary endpoints for all doses are presented to allow complete and robust clinical assessment of the study information.

The key secondary efficacy endpoints are to be tested in order as follows:

- change from baseline to end of treatment in WHO functional class,
- time to clinical worsening, and
- change from baseline to end of treatment in Borg dyspnea score.

Other efficacy endpoints included hemodynamic parameters obtained in a subset of patients by right heart catheterization and QoL parameters (SF-36v2 and EuroQoL).

WHO Functional Class

Most subjects were WHO functional class II and III at baseline. There was fairly even distribution among the treatment groups. The majority of subjects had no change in their WHO functional class after 16 weeks of treatment⁷. There were no statistically significant differences between any tadalafil treatment group compared to placebo in incidences of WHO functional class improvement, no change, or worsening. However, tadalafil 40 mg group had a lower incidence of worsening (10%) compared to placebo (16%) and the other active treatment groups.

As tadalafil 40 mg group was not statistically significantly better than placebo (p=0.36) relative to WHO functional class, no statistical testing of other secondary endpoints should be performed. We present results for all secondary endpoints and all doses only to allow complete and robust assessment of the study.

⁷ At week 16, there is a large number of subjects without WHO functional class data

Number and (percent) of subjects: Change from baseline at week 16

WHO functional class	Placebo n=82	Tadalafil			
		2.5 mg n=82	10 mg n=80	20 mg n=82	40 mg n=79
No change	52 (63)	43 (52)	50 (63)	37 (45)	53 (67)
worsen	13 (16)	18 (22)	11 (14)	15 (18)	8 (10)
Improved	17 (21)	21 (26)	19 (24)	30 (37)	18 (23)
P value+		0.97	0.58	0.17	0.36

+Cochran-Mantel-Haenszel test stratified by PAH etiology, bosentan use, and baseline 6-minute walk distance compared to placebo.

Clinical worsening

Clinical worsening was defined in the study protocol as any of the following: death, lung transplantation, atrial septostomy, hospitalization because of worsening PAH, initiation of new PAH therapy (prostacyclin or analog, endothelin receptor antagonist, PDE5 inhibitor), or worsening WHO functional class⁸.

The numbers of subjects who met one of these endpoints during the trial are shown below by treatment group.

Number and (percent) of subjects

	Placebo n=82	Tadalafil			
		2.5 mg n=82	10 mg n=80	20 mg n=82	40 mg n=79
Total with clinical worsening	13 (16)	10 (12)	7 (9)	8 (10)	4 (5)
death	1	0	1	0	0
Hosp. for worsening PAH	2	2	3	0	1
New PAH rx	0	1	0	2	1
Worsening WHO class	11	10	6	6	3

Tadalafil 40 mg had fewer subjects who reported clinical worsening compared to the other treatment groups. This was primarily the result of fewer subjects reporting worsening of WHO functional class.

⁸ The first table on this page made the assumption that subjects with no week 16 data were considered as "worsened" from baseline; no such assumption was made for the second table".

The Kaplan-Meier curves for time to clinical worsening (placebo and all doses of tadalafil) are shown below.

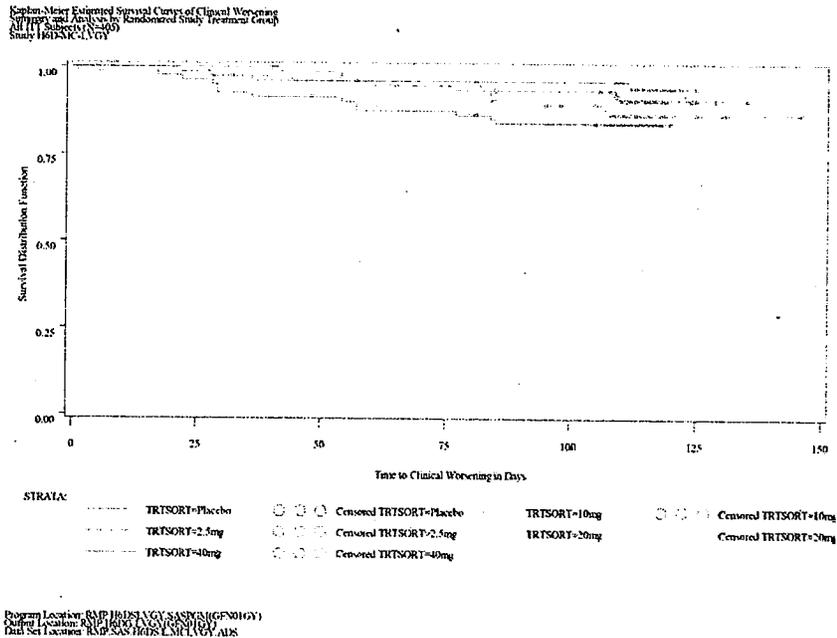


Figure LVGY.11.3. Kaplan-Meier survival curves for time to clinical worsening.

Borg dyspnea score

The mean Borg dyspnea scores at baseline ranged from 3.86 to 4.07. At endpoint, the tadalafil 40 mg group had the largest improvement in the Borg score.

Cardiopulmonary hemodynamics

There were 93 subjects who participated in the cardiopulmonary hemodynamic substudy. The tadalafil 40 mg group showed improvements from baseline in mPAP, PVR, CI, and CO.

Health outcomes/Quality of life evaluations

The SF-36v2 Health Survey evaluates 8 domains (physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, and mental health). Tadalafil seemed to improve most of these domains with the most improved scores displayed in the 40 mg dose.

Improvements in the tadalafil groups were also shown in the EuroQoL Questionnaire which consists of 5 questions (mobility, self care, usual activities, pain/discomfort, anxiety/depression) as well as a visual analog scale to rate global health related QoL. Again, tadalafil 40 mg group displayed the most improvement.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

More than 18,400 subjects have been exposed to tadalafil during the development of CIALIS® for ED (majority of subjects were exposed to doses up to 20 mg) and for PAH (subjects were exposed to doses up to 40 mg once daily).

As of September 2007, approximately _____ patients have been exposed to tadalafil worldwide.

b(6)(4)

There was one placebo controlled trial (LVGY) examining the use of tadalafil in PAH. The other clinical trial with PAH patients was an open label, uncontrolled extension trial (LVGX). The five clinical pharmacology studies included only healthy volunteers. A compassionate use study LVHU is ongoing with 1 patient enrolled.

A summary of the safety results include:

- 1) commonly reported adverse events were similar regardless of indication.
- 2) from the available data, there is no special safety concerns with any of the subgroups that were studied.
- 3) doses of 40 mg were tolerated by most subjects for up to one year in an uncontrolled clinical trial. Safety data indicate that tadalafil 20 and 40 mg are reasonably safe and well tolerated for long-term treatment of PAH.
- 4) warnings section in package label for phosphodiesterase type-5 inhibitors (e.g., sildenafil) include statements about possible mild and transient decreases in blood pressure and worsening cardiovascular status of patients with pulmonary veno-occlusive disease. These warnings should be included in the package label for tadalafil.
- 5) Selected reported adverse events (bleeding including menorrhagia, cardiac events, ear and labyrinth disorders, eye disorders, musculoskeletal and connective tissue disorders, reproductive and breast disorders) were examined and did not reveal any additional information about the safety of tadalafil.
- 6) Adverse event profiles were similar regardless of gender and age.
- 7) Subjects with severe renal impairment (creatinine clearance < 30 mL/minute were excluded from the trials. Those subjects with mild or moderate renal impairment did not appear to be different in reported adverse events compared to those with normal renal function.

8) Subjects who were taking concomitant bosentan tended to report dyspepsia more often than those not taking bosentan. And, as expected, there were more reports of liver enzyme elevations in the concomitant bosentan group compared to the group taking only tadalafil.

Exposure

LVGY

A total of 320 subjects received tadalafil during the placebo controlled trial LVGY. Of the 320 subjects, 282 were treated for at least 12 weeks. The tadalafil 40 mg group included 72 subjects treated for at least 12 weeks. The uncontrolled extension trial LVGX included exposure data for 352 subjects with 266 subjects receiving tadalafil for at least 6 months and 82 (26 taking 40 mg) receiving tadalafil for at least 12 months.

LVGX

There were 357 subjects who had been enrolled into LVGY and entered the open label extension trial LVGX. Of these 357 subjects, 352 received tadalafil (62 received 20 mg and 290 received 40 mg). A total of 266 subjects had at least 6 months exposure to tadalafil and 82 subjects had at least 12 months exposure.

Subject Disposition

LVGY

The numbers of subjects with various trial outcomes are shown below by treatment group.

Number and (%) of subjects

	Placebo	tadalafil			
		2.5 mg	10 mg	20 mg	40 mg
randomized	82	82	81	82	79
completed week 16	69 (84)	64 (78)	71 (89)	66 (80)	71 (90)
early dc'd	13 (16)	18 (22)	9 (11)	16 (20)	8 (10)
died	1 (1)	0	1 (1)	0	0
dc'd for adverse event	12 (15)	13 (16)	6 (8)	9 (11)	7 (9)
dc'd because of invest decision	0	0	0	3	0
Lost to follow up	0	0	1 (1)	0	0
dc'd because of protocol not met	0	0	0	2 (2)	0
dc'd because of needing other PAH meds	0	0	0	2 (2)	1 (1)
withdrew consent	0	5 (6)	1 (1)	0	0

Table 10.1

A somewhat higher percentage of tadalafil 40 mg group (90%) completed week 16 compared to the other groups. The tadalafil 2.5 mg group had the lowest percentage of completers (78%).

There were 2 deaths (placebo and 10 mg).

The majority of premature drop outs were reported to have occurred because of adverse event(s). The placebo group had the greatest percentage of drop outs for this reason (15%) and tadalafil 10 mg had the lowest (8%).

The reasons given for those who withdrew because of adverse events are shown below.

Number and (percent) of subjects

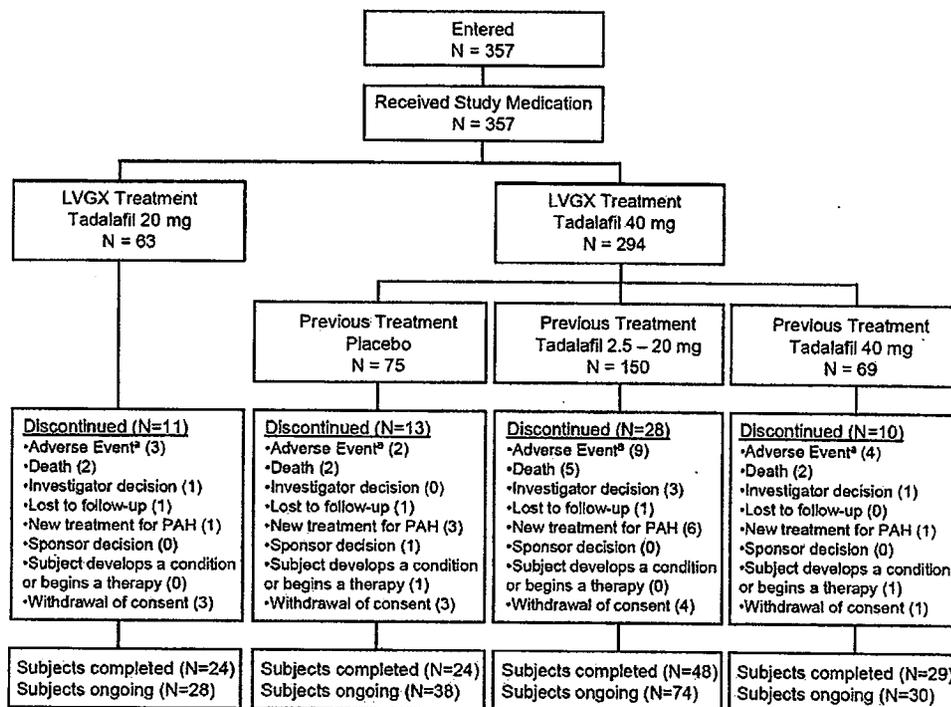
	Placebo	tadalafil			
		2.5 mg	10 mg	20 mg	40 mg
Total randomized	82	82	81	82	79
Total dc'd for AE	12 (15)	13 (16)	6 (8)	9 (11)	7 (9)
Hosp. for worsening PAH	1 (1)	1 (1)	1 (1)	0	1 (1)
Worsening of WHO functional class	7 (9)	7 (9)	2 (3)	4 (5)	3 (4)
Other AE	4 (5)	5 (6)	3 (4)	5 (6)	3 (4)

There were 4 hospitalizations for worsening PAH, evenly distributed among the treatment groups (except for tadalafil 20 mg which had none). The highest percentages of subjects with worsening WHO functional class were in the placebo and tadalafil 2.5 mg groups.

Drop outs for "other adverse events" were nearly evenly distributed across treatment groups.

LVGX

Of the 357 subjects who entered the extension study and received study drug, 63 (18%) received tadalafil 20 mg and 294 (82%) received tadalafil 40 mg. There were 62 subjects who discontinued the study early, 125 who completed the 52-week phase, and 170 who are still participating in the trial. As of the cut off date, there were 11 reported deaths, 5 discontinuations because of investigator decision, 3 lost to follow up, 4 discontinuations because of hospitalization for worsening PAH, 1 for severe renal insufficiency, and 2 for worsening WHO functional class.



Abbreviations: N = number of subjects; PAH = pulmonary arterial hypertension; WHO = World Health Organization.

^a Adverse events (AEs) that led to discontinuation were hospitalization due to worsening of PAH, severe renal insufficiency, worsening of WHO functional class, and/or other AEs.

There were 19 subjects who entered Study LVGX with clinical worsening reported during the base study LVGY. Of these, 6 completed Part 1, 4 are continuing in Part 1, 3 died, 3 discontinued because of receiving new chronic PAH treatment, and 3 discontinued because of an adverse event.

The subjects experiencing death, serious adverse events, discontinuation because of an adverse event and treatment emergent adverse events are shown in the table below.

**Table LVGX.8.3. Overview of Adverse Events
Study Treatment and Study Treatment in Previous Study
All Subjects Who Entered and Received Study Treatment**

Adverse Event ^a	T20 (N=63)	T40 P:Pla (N=75)	T40 P:T2.5-20 (N=150)	T40 P:T40 (N=69)	All T40 (N=294)	TOTAL (N=357)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Deaths ^b	2 (3.2)	2 (2.7)	5 (3.3)	2 (2.9)	9 (3.1)	11 (3.1)
Serious Adverse Events	13 (20.6)	20 (26.7)	40 (26.7)	10 (14.5)	70 (23.8)	83 (23.2)
Discontinuations due to an Adverse Event	5 (7.9)	4 (5.3)	14 (9.3)	6 (8.7)	24 (8.2)	29 (8.1)
Treatment Emergent Adverse Events	56 (88.9)	64 (85.3)	131 (87.3)	61 (88.4)	256 (87.1)	312 (87.4)

Abbreviations: N = number of entered subjects who have received study medication; n = number of subjects per category; TRAE = treatment-emergent adverse event; Prev = Actual received study treatment in previous placebo-control double-blind study; P = Prev; T2.5-20 = Tadalafil 2.5-20mg; T20 = Tadalafil 20mg; T40= Tadalafil 40mg.

^a - Subjects may be counted in more than one category.

^b - Deaths are also included as serious adverse events and discontinuations due to adverse events.

^c - Includes events that were considered possibly related to study drug as judged by the investigator.

There were 11 (3%) deaths reported during the extension study. There were 83 subjects who reported one or more serious adverse events and 29 subjects who discontinued study drug because of an adverse event (s). Nearly all patients (87%) reported at least one adverse event.

The tadalafil 20 mg (n=63) and the 40 mg (n=69) groups were similar in the reporting of deaths, discontinuations for adverse events and treatment emergent adverse events. The reporting of serious adverse events, however, was somewhat more frequent in the tadalafil 20 mg group (21% compared to 15%).

7.1.1 Deaths

LVGY

There were 3 reported deaths. These subjects are discussed below.

Deaths

ID/drug/dose	Days on drug	Cause of death
138 2854/tad/10 mg	109	Sudden death
912 8701/tad/20 mg	14	Hematophagic histiocytosis
128 2362/placebo/na	53	Pulmonary hypertension

Subject 138 2854 was a 73 year old female with a medical history of Sjogren's scleroderma, Raynaud's, headaches, anxiety, depression, retinal inflammation, seasonal allergies, sinus congestion, hiatal hernia, peptic ulcer, diverticulitis, irritable bowel syndrome, and esophageal stricture. She was receiving concomitant alprazolam, escitalopram, esomeprazole, prednisolone, triamcinolone, loperamide, and fexofenadine. About 3 months after start of study drug, the subject presented with facial drooping, facial spasms and slurred speech. Bell's Palsy was diagnosed. After 15 weeks of being on study drug, the patient's daughter reported that the subject awakened complaining of a severe headache and intense body flushing. She became

comatose and unresponsive (study day 109). Emergency personnel was unable to revive the patient. No autopsy was performed, and the cause of death was listed as sudden death (cause unknown).

Subject 912 8701 was a 28-year old female who developed PAH secondary to systemic lupus erythematosus and Sjogren's syndrome. PAH was severe but controlled and stabilized by medication therapy with steroids. She was also suffering from osteoporosis and bilateral osteonecrosis of the femoral head.

Subject developed a headache one day after starting study drug. Shortly thereafter, she reported eyelid edema and eyelid pain. No abnormality was found and cyanocobalamin eye drops was prescribed. About one week after starting study drug the subject reported malaise. She became febrile and reported to the hospital with anorexia and malaise. CAT scan findings revealed pleural effusion. WBC and bacteria were noted in urine culture. Antibiotics were started and study drug was stopped. She was suspected to have developed TTP and hemophagocytic syndrome⁹ (HPS) and started therapy with methylprednisolone and hydrocortisone. Her health continued to decline and she was sent to the ICU with difficulty breathing, pleural effusion, decreasing blood pressure, a bleeding tendency and drop in platelet count. Bone marrow aspiration showed patchy hemophagocytosis. HPS associated with SLE was suspected. The subject died three days after discontinuing the study drug.

The autopsy revealed hemorrhagic lesions in various tissues and signs of steroid treatment. The cause of the death was considered to be the underlying pulmonary hypertension and cardiac failure. Although the biopsy revealed no hemophagocytosis, significant hemophagocytosis had been reported in the bone marrow when she was admitted to the hospital.

The third death occurred in a subject randomized to placebo.

LVGX

The eleven subjects who were reported to have died during the extension study (up to) are shown in the table below. All but 2 had been on tadalafil 40 mg at the time of death.

b(6)

⁹ Hematophagic histiocytosis generally occurs in patients who develop infections in the setting of preexisting immunologic abnormalities or neoplasms. Viral infections are most commonly involved, but virtually any other infectious agent can precipitate this syndrome.

Table LVGX.8.4. Deaths
Listing of All Subjects
All Subjects Who Entered and Received Study Treatment

Inv	Sub	Trt	Prev Trt	Cause of Death (Preferred Term)	Date of Death	Date of Randomization	Study day
114	1661	Tadalafil 40mg	Tadalafil 10mg	LUNG ADENOCARCINOMA			169
115	1701	Tadalafil 40mg	Tadalafil 10mg	PNEUMONIA			11
120	1954	Tadalafil 40mg	Placebo	CARDIAC ARREST			9
127	2301	Tadalafil 20mg	Tadalafil 20mg	DEATH			260
132	2556	Tadalafil 40mg	Tadalafil 2.5mg	MYOCARDIAL INFARCTION			140
201	4004	Tadalafil 40mg	Tadalafil 10mg	RIGHT VENTRICULAR FAILURE			8
503	5701	Tadalafil 40mg	Tadalafil 2.5mg	RIGHT VENTRICULAR FAILURE			210
505	5801	Tadalafil 40mg	Tadalafil 40mg	PNEUMONIA			38
601	6602	Tadalafil 20mg	Tadalafil 20mg	SUDDEN DEATH			141
601	6617	Tadalafil 40mg	Placebo	SUDDEN CARDIAC DEATH			160
601	6621	Tadalafil 40mg	Tadalafil 40mg	SUDDEN CARDIAC DEATH			4

Abbreviations: N = number of entered subjects who have received study medication; Inv = Investigator; Sub = Subject; Trt = Actual received study treatment; Prev Trt = Actual received study treatment in previous placebo-control double-blind study.

b(6)

Of the subjects who died, there were 4 reports of sudden deaths/cardiac arrest, 2 reports of right ventricular failures, 2 reports of pneumonia, 1 myocardial infarction, 1 reported as death¹⁰, and 1 lung carcinoma. All but 2 had been taking tadalafil during the base study.

Subject 601 6621 experienced sudden death after 4 days in the extension study. He had been on 40 mg during the base study.

Subject 120 1954 experienced cardiac arrest after 9 days in the extension study. This was a 52 year old female with scleroderma, Sjogren's disease, rheumatoid arthritis, Raynaud's syndrome, Hashimoto's thyroiditis and chronic inflammatory demyelinating paraneuropathy. She had been hospitalized for diarrhea and pedal edema during the base study. One week after receiving the first dose of tadalafil in the extension study, she was hospitalized for deterioration. The subject died from cardiac arrest nine days after starting tadalafil 40 mg. She had been randomized to placebo during the base study.

Subject 201 4004 experienced right ventricular failure after 8 days in the extension study. He had been on tadalafil 10 mg during the base study.

Subject 132 2556 was a 40 year old female with a history of multiple myeloma. She was discontinued from study drug after she developed renal failure. She died of multi-organ failure about one month later.

The remaining deaths were reported in subjects who had died of pneumonia (2) or had been on study drug at least 141 days.

Other deaths

There were no deaths reported in the clinical pharmacology studies.

¹⁰ Found dead at home, possible suicide, no other details available.

7.1.2 Serious adverse events

LVGY

The numbers of subjects reporting at least one serious adverse event are shown below by treatment group.

Serious adverse event reports: no. of subjects and (percent)

	tadalafil			
Placebo n=82	2.5 mg n=82	10 mg n=80	20 mg n=82	40 mg n=79
12 (15)	14 (17)	10 (13)	11 (13)	7 (9)

The treatment group with the highest percentage of serious adverse events is tadalafil 2.5 mg (17%) followed by placebo (15%). Tadalafil 40 mg has the lowest (9%).

Serious adverse events reported by at least 2 tadalafil subjects are shown below.

No. and (percent) of subjects

	tadalafil				
Serious event	Placebo n=82	2.5 mg n=82	10 mg n=80	20 mg n=82	40 mg n=79
Pulmonary hypertension	1 (1)	4 (5)	3 (4)	0	2 (3)
R ventricular failure	1 (1)	2 (2)	2 (3)	1 (1)	0
Anemia	0	2 (2)	0	1 (1)	0
Dyspnea	0	1 (1)	1 (1)	1 (1)	0
URI	0	1 (1)	0	1 (1)	0

These serious adverse events are not unexpected in this population.

LVGX

Serious adverse events reported by at least 2 tadalafil subjects are shown below.

Table LVGX.8.5. Serious Adverse Events by Preferred Term in Descending Order of Incidence Study Treatment and Study Treatment in Previous Study All Subjects Who Entered and Received Study Treatment

Preferred Term	T20 (N=63) n (%)	T40 P:Pla (N=75) n (%)	T40 P:T2.5-20 (N=150) n (%)	T40 P:T40 (N=63) n (%)	All T40 (N=294) n (%)	TOTAL (N=357) n (%)
Patients with >= 1 Serious AE	13 (20.6)	20 (26.7)	40 (26.7)	10 (14.5)	70 (23.8)	83 (23.2)
PULMONARY HYPERTENSION	1 (1.6)	2 (2.7)	4 (2.7)	2 (2.9)	9 (2.7)	9 (2.5)
RIGHT VENTRICULAR FAILURE	0 (0.0)	5 (6.7)	3 (2.0)	1 (1.4)	9 (3.1)	9 (2.5)
PNEUMONIA	0 (0.0)	0 (0.0)	4 (2.7)	2 (2.9)	6 (2.0)	6 (1.7)
CHEST PAIN	1 (1.6)	0 (0.0)	3 (2.0)	1 (1.4)	4 (1.4)	5 (1.4)
ANAEMIA	1 (1.6)	1 (1.3)	1 (0.7)	0 (0.0)	2 (0.7)	3 (0.8)
NON-CARDIAC CHEST PAIN	1 (1.6)	1 (1.3)	1 (0.7)	0 (0.0)	2 (0.7)	3 (0.8)
OEDEMA PERIPHERAL	0 (0.0)	1 (1.3)	2 (1.3)	0 (0.0)	3 (1.0)	3 (0.8)
ANGINA PECTORIS	1 (1.6)	0 (0.0)	0 (0.0)	1 (1.4)	1 (0.3)	2 (0.6)
ARTERIALGIA	1 (1.6)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.3)	2 (0.6)
CARDIAC FAILURE	0 (0.0)	2 (2.7)	0 (0.0)	0 (0.0)	2 (0.7)	2 (0.6)
DEHYDRATION	1 (1.6)	1 (1.3)	0 (0.0)	0 (0.0)	1 (0.3)	2 (0.6)
DIABETES MELLITUS	1 (1.6)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.3)	2 (0.6)
DIARRHOEA	1 (1.6)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.3)	2 (0.6)
DYSPNOEA	1 (1.6)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.3)	2 (0.6)
GASTROINTESTINAL HAEMORRHAGE	1 (1.6)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.3)	2 (0.6)
HAEMOPTYSIS	0 (0.0)	0 (0.0)	2 (1.3)	0 (0.0)	2 (0.7)	2 (0.6)
OSTEOARTHRITIS	1 (1.6)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.3)	2 (0.6)
PAIN IN EXTREMITY	1 (1.6)	1 (1.3)	0 (0.0)	0 (0.0)	1 (0.3)	2 (0.6)
PALPITATIONS	1 (1.6)	0 (0.0)	0 (0.0)	1 (1.4)	1 (0.3)	2 (0.6)
PLEURAL EFFUSION	0 (0.0)	0 (0.0)	2 (1.3)	0 (0.0)	2 (0.7)	2 (0.6)
SUDDEN CARDIAC DEATH	0 (0.0)	1 (1.3)	0 (0.0)	1 (1.4)	2 (0.7)	2 (0.6)

Abbreviations: N = number of entered subjects who have received study medication; n = number of subjects with at least one serious adverse event; Prev = Actual received study treatment in previous placebo-control double-blind study; P = Prev; T2.5-20 = Tadalafil 2.5-20mg; T20 = Tadalafil 20mg; T40= Tadalafil 40mg.

Commonly reported serious adverse events included pulmonary hypertension (9), right ventricular failure (9), pneumonia (6), and chest pain (5). Events reported by 3 subjects included anemia, non-cardiac chest pain, and peripheral edema. These are serious events frequently reported by this type of subject population.

There was one report each of renal failure, acute renal failure, toxic hepatitis, and pancreatitis.

Renal failure

132 2556 This was a 40 year old white female whose past medical history included scleroderma, hypertension, reflux esophagitis, diarrhea, multiple myeloma, Raynaud's phenomenon, multiple myeloma, and depression. Concomitant medications included bosentan, warfarin, hydroxychloroquine, gabapentin, bupropion, lisinopril, rabeprazole, mupirocin, levofloxacin, and codeine/paracetamol. The subject was found to have renal insufficiency with a creatinine of 6.4 mg/dL and a BUN of 50 mg/dL. Upon review of past laboratory results, the investigator found her to have had increasing creatinine levels (1.3 mg/dL eight months previously). Dialysis was recommended. She was seen by the investigator one week later and was admitted for renal failure. Multiple renal cysts were found on ultrasound and biopsy findings were consistent with acute and chronic thrombotic microangiopathy, probably related to sclerodermal renal disease. Study drug was discontinued. She died about one month later of myocardial infarction/multi-organ failure.

Acute renal failure

702-6901 This was an 87 year old female with a history of diabetes mellitus type I, chronic glaucoma, optic neuropathy, atrial fibrillation, pulmonary hypertension grade I, and acute tricuspid insufficiency grade II with moderate dilatation of the right atrium. Concomitant medications included nifedipine, spironolactone, bosentan,

acenocoumarol, gliclazider, and digoxin. The subject was hospitalized 133 days after beginning tadalafil because of acute lithiasis cholecystitis. Acute renal failure was reported ten days later. A cholecystectomy was performed successfully. Final diagnosis included acute lithiasis cholecystitis, normocytic anemia and chronic renal insufficiency.

Toxic hepatitis

601 6605 This was a 28 year-old female subject with concomitant medications including bosentan, nifedipine, furosemide, potassium canrenoate, digoxin, warfarin sodium. Approximately nine months after receiving the first dose of tadalafil, she experienced toxic hepatitis with nausea and subicterus. The patient was hospitalized with elevated hepatic enzymes. Bosentan was discontinued and the subject recovered.

Elevated liver enzymes and low creatinine clearance

129 2403. This was a 74 year old taking concomitant bosentan.

Other studies

There were three serious adverse events reported by a subject receiving tadalafil during a clinical pharmacology study: angina pectoris (5 mg), pneumothorax (40 mg), spinal laminectomy (5 mg).

7.1.3 Discontinuations because of adverse events

LVGY

Discontinuations because of adverse event: no. of subjects and (percent)

Placebo n=82	Tadalafil			
	2.5 mg n=82	10 mg n=80	20 mg n=82	40 mg n=79
13 (16)	13 (16)	7 (9)	9 (11)	7 (9)

The 2 drug groups with the highest percentage of discontinuations for adverse events were placebo and tadalafil 2.5 mg (both 16%).

Adverse events leading to discontinuations by at least 2 tadalafil subjects are shown below.

No. and (percent) of subjects

event	Placebo n=82	tadalafil			
		2.5 mg n=82	10 mg n=80	20 mg n=82	40 mg n=79
Pulmonary hypertension	7 (8)	4 (5)	2 (3)	4 (5)	3 (4)
Back pain	0	0	1 (1)	0	1 (1)
Dyspnea	1 (1)	2 (2)	0	0	0
R ventricular failure	0	1 (1)	1 (1)	0	0

Other events leading to discontinuation included drug hypersensitivity (tadalafil 40 mg) and pregnancy (tadalafil 40 mg) resulting in a normal birth. There was one discontinuation for neutropenia: Subject 603 6702 discontinued at visit 6 (neutrophils thousands/microliter visit 2: 1.9 and visit 6: 0.9; leucocyte count fell from 4.14 to 2.96).

LVGX

There were 29 subjects who discontinued study drug because of an adverse event. Adverse events that led to discontinuation in more than one subject included pulmonary hypertension (4), right ventricular failure (4), pneumonia (2), and sudden cardiac death (2).

Other studies

There were 35 subjects in a clinical pharmacology study who discontinued study drug because of an adverse event. The events reported by at least 3 subjects were nausea (9 total, 8 with the 20 mg dose), headache (8 total, 4 with the 40 mg dose, vomiting (5, 4 total with the 20 mg dose), and back pain (3 total, 2 with the 20 mg dose).

7.1.5 Common Adverse Events

LVGY

The adverse events reported by at least five subjects randomized to tadalafil 40 mg and reported by fewer subjects randomized to placebo are shown below by treatment group.

Adverse event reporting: no. and (percent) of subjects

event	Placebo n=82	tadalafil			
		2.5 mg n=82	10 mg n=80	20 mg n=82	40 mg n=79
Any event	65 (79)	72 (88)	72 (90)	69 (84)	75 (95)
Headache	12 (15)	15 (18)	30 (38)	26 (32)	33 (42)
Myalgia	3 (4)	2 (2)	3 (4)	7 (9)	11 (14)
Flushing	2 (2)	3 (4)	5 (6)	5 (6)	10 (13)
Nasopharyngitis	6 (7)	4 (5)	6 (8)	2 (2)	10 (13)
Diarrhea	8 (10)	9 (11)	9 (11)	6 (7)	9 (11)
Nausea	5 (6)	6 (7)	7 (9)	8 (10)	9 (11)
Pain in extremity	2 (2)	3 (4)	4 (5)	4 (5)	9 (11)
Back pain	5 (6)	5 (6)	5 (6)	10 (12)	8 (10)
Dyspepsia	2 (2)	4 (5)	2 (3)	11 (13)	8 (10)
Nasal congestion	1 (1)	3 (4)	3 (4)	0	7 (9)
Chest pain/chest discomfort	4 (5)	6 (7)	2 (3)	8 (10)	7 (9)
Dyspnea	3 (4)	8 (10)	4 (5)	4 (5)	5 (6)
Vomiting	1 (1)	2 (2)	2 (3)	6 (7)	5 (6)
Fatigue	3 (4)	4 (5)	1 (1)	4 (5)	5 (6)

LVGY.12.3

Adverse events most commonly reported by the tadalafil 40 mg group include headache, myalgia, flushing, and nasopharyngitis (placebo subtracted incidence rates were 27%, 10%, 11%, and 6%, respectively).

The reporting of nausea could possibly be dose related. Placebo subtracted incidence rates were 1.2% tadalafil 2.5 mg, 2.7 % tadalafil 10 mg, 3.7 % tadalafil 20 mg, 4.9% tadalafil 40 mg. Most were reported as mild.

Compared to placebo, there were twice as many tadalafil subjects reporting musculoskeletal and connective tissue disorders including arthralgia, back pain, myalgia, and pain in extremity. The placebo subtracted rate for reporting all events in this body system was 14% with most events reported as mild or moderate.

While there were no reports of menorrhagia/vaginal hemorrhage reported in the placebo group, the tadalafil groups had 8 reports (2%). Most were reported as mild or moderate.

LVGX

Adverse events reported by at least 3% of the total tadalafil subjects are shown below

Table LVGX.8.8. Treatment-Emergent Adverse Events Occurring in Greater than or Equal to 3.0% of Subjects in Preferred Term in Descending Order of Incidence Comparison of Treatment Groups All Subjects Who Entered and Received Study Treatment

Preferred Term	T20 (N=63) n (%)	T40 P:Pla (N=75) n (%)	T40 P:T2.5-20 (N=150) n (%)	T40 P:T40 (N=69) n (%)	All T40 (N=294) n (%)	TOTAL (N=357) n (%)
Patients with ≥ 1 TEAE						
HEADACHE	9 (14.3)	21 (28.0)	37 (24.7)	10 (14.5)	68 (23.1)	77 (21.6)
DIARRHOEA	5 (7.9)	6 (8.0)	18 (12.0)	9 (13.0)	33 (11.2)	38 (10.6)
BACK PAIN	2 (3.2)	11 (14.7)	17 (11.3)	5 (7.2)	33 (11.2)	35 (9.8)
OEDEMA PERIPHERAL	5 (7.9)	7 (9.3)	17 (11.3)	5 (7.2)	30 (10.2)	35 (9.8)
UPPER RESPIRATORY TRACT INFECTION	7 (11.1)	5 (6.7)	13 (8.7)	9 (13.0)	27 (9.2)	34 (9.5)
DIZZINESS	2 (3.2)	4 (5.3)	20 (13.3)	3 (4.3)	31 (10.5)	33 (9.2)
PALPITATIONS	3 (4.8)	8 (10.7)	19 (12.7)	5 (7.2)	28 (9.5)	31 (8.7)
DYSPNOEA	5 (7.9)	5 (6.7)	13 (8.7)	7 (10.1)	25 (8.5)	30 (8.4)
PULMONARY HYPERTENSION	2 (3.2)	5 (6.7)	12 (8.0)	8 (11.6)	25 (8.5)	27 (7.6)
DYSPEPSIA	5 (7.9)	5 (6.7)	12 (8.0)	3 (4.3)	20 (6.8)	25 (7.0)
PAIN IN EXTREMITY	5 (7.9)	7 (9.3)	10 (6.7)	2 (2.9)	19 (6.5)	24 (6.7)
COUGH	3 (4.8)	7 (9.3)	7 (4.7)	6 (8.7)	20 (6.8)	23 (6.4)
NASOPHARYNGITIS	2 (3.2)	8 (10.7)	6 (4.0)	7 (10.1)	21 (7.1)	23 (6.4)
NAUSEA	3 (4.8)	4 (5.3)	10 (6.7)	6 (8.7)	20 (6.8)	23 (6.4)

Preferred Term	T20 (N=63) n (%)	T40 P:Pla (N=75) n (%)	T40 P:T2.5-20 (N=150) n (%)	T40 P:T40 (N=69) n (%)	All T40 (N=294) n (%)	TOTAL (N=357) n (%)
FATIGUE	3 (4.8)	4 (5.3)	7 (4.7)	8 (11.6)	19 (6.5)	22 (6.2)
INSOMNIA	4 (6.3)	5 (6.7)	7 (4.7)	5 (7.2)	17 (5.8)	21 (5.9)
CHEST PAIN	3 (4.8)	3 (4.0)	8 (5.3)	6 (8.7)	17 (5.8)	20 (5.6)
RHINITIS	5 (7.9)	5 (6.7)	8 (5.3)	2 (2.9)	15 (5.1)	20 (5.6)
FLUSHING	3 (4.8)	8 (10.7)	5 (3.3)	4 (5.8)	17 (5.8)	20 (5.6)
ANASHTIA	3 (4.8)	3 (4.0)	10 (6.7)	1 (1.4)	14 (4.8)	17 (4.8)
NASAL CONGESTION	1 (1.6)	5 (6.7)	5 (3.3)	6 (8.7)	16 (5.4)	17 (4.8)
VISION BLURRED	5 (7.9)	4 (5.3)	6 (4.0)	2 (2.9)	12 (4.1)	17 (4.8)
MYALGIA	4 (6.3)	5 (6.7)	4 (2.7)	3 (4.3)	12 (4.1)	16 (4.5)
RASH	4 (6.3)	5 (6.7)	3 (2.0)	4 (5.8)	12 (4.1)	16 (4.5)
MUSCLE SPASMS	3 (4.8)	2 (2.7)	8 (5.3)	2 (2.9)	12 (4.1)	15 (4.2)
ARTHRALGIA	1 (1.6)	2 (2.7)	10 (6.7)	1 (1.4)	13 (4.4)	14 (3.9)
DEPRESSION	2 (3.2)	4 (5.3)	3 (2.0)	4 (5.8)	11 (3.7)	13 (3.6)
HYPOTALAEMIA	1 (1.6)	3 (4.0)	4 (2.7)	4 (5.8)	11 (3.7)	12 (3.4)
SINUSITIS	1 (1.6)	2 (2.7)	6 (4.0)	3 (4.3)	11 (3.7)	12 (3.4)
URINARY TRACT INFECTION	1 (1.6)	6 (8.0)	3 (2.0)	2 (2.9)	11 (3.7)	12 (3.4)
WEIGHT INCREASED	3 (4.8)	1 (1.3)	4 (2.7)	4 (5.8)	9 (3.1)	12 (3.4)

Preferred Term	T20 (N=63) n (%)	T40 P:Pla (N=75) n (%)	T40 P:T2.5-20 (N=150) n (%)	T40 P:T40 (N=69) n (%)	All T40 (N=294) n (%)	TOTAL (N=357) n (%)
ANXIETY	1 (1.6)	3 (4.0)	5 (3.3)	2 (2.9)	10 (3.4)	11 (3.1)
BRONCHITIS	2 (3.2)	1 (1.3)	4 (2.7)	4 (5.8)	9 (3.1)	11 (3.1)
OEDEMA	3 (4.8)	0 (0.0)	5 (3.3)	3 (4.3)	8 (2.7)	11 (3.1)

Abbreviations: N = number of entered subjects who have received study medication; n = number of subjects with at least 1 TEAE; TEAE = treatment-emergent adverse event; Prev = Actual received study treatment in previous placebo-control double-blind study; P = Prev; T2.5-20 mg = Tadalafil 2.5-20 mg; T20 = Tadalafil 20 mg; T40 = Tadalafil 40 mg.
 * Subjects may be counted in more than 1 category. Baseline is the run-in period (Visit 1-2) prior to randomization in the previous placebo-controlled double-blind study.

The most commonly reported events included headache (22%), diarrhea (11%), back pain (10%), peripheral edema (10%), URI (10%). Many of the events are included in the adverse events reported for the erectile dysfunction indication (headache, dyspepsia, back pain, myalgia, nasal congestion, flushing, and pain in limb)

7.1.7 Laboratory Findings

LVGY and LVGX

Discontinuations because of abnormal lab value (s)

The following abnormal lab values led to subject withdrawal: liver function test (LVGX 129 2403 tadalafil 20 mg), increased creatinine clearance (LVGX 503 5706 tadalafil 40 mg), and neutropenia (LVGY 603 6702 tadalafil 10 mg¹¹).

¹¹ Subject 603 6702 discontinued for neutropenia (neutrophils thousands/microliter visit 2: 1.9 and visit 6: 0.9; leucocyte count fell from 4.14 to 2.96).

LVGY

Abnormal lab values

There were a few subjects with > 3 times the upper limit of normal (ULN) for ALT (2 placebo, and one each tadalafil 2.5 mg, tadalafil 10 mg, tadalafil 20 mg) or for AST (2 placebo, and one each tadalafil 2.5 mg, tadalafil 10 mg, tadalafil 20 mg, and tadalafil 40 mg). Liver enzyme elevations >5 times the ULN for serum ALT included one each placebo, tadalafil 2.5 mg, and tadalafil 10 mg; for serum AST there were 2 placebo and one tadalafil 2.5 mg.

There were few subjects with platelet counts >100 GI/L at baseline and at any post baseline visit:

- <100 GI/L (four placebo, one tadalafil 2.5 mg, and two tadalafil 40 mg),
- <75 GI/L (placebo),
- <50 GI/L (placebo), or
- <20 GI/L (placebo).

There was one report of serious hypokalemia (123 2108 tadalafil 20 mg), one report of serious hematocrit/hemoglobin decrease (121 2002 tadalafil 2.5 mg), and three reports of serious anemia (128 2353 and 129 2405 tadalafil 2.5 mg; 129 2403 tadalafil 20 mg).

LVGX

Clinical laboratory values

Hematology

There were 3 serious adverse event reports of anemia (502-5655, 506-5851, 509-6002). None led to study drug discontinuation.

Renal function

There was one discontinuation for increased creatinine (503-5706).

Liver function

There was one discontinuation for abnormal liver function tests (129 2403, subject was taking bosentan).

Two subjects (303-4302 and 601-6605) reported >5 times ULN for both serum AST and ALT; both subjects were taking bosentan.

Subject 601-6601 had >3 times ULN for serum AST and >5 times ULN for serum ALT.

Subject 601-6616 had >3 times ULN for both serum AST and ALT.

Subject 118-1854 had >5 times ULN for serum AST; subject discontinued prematurely because of peripheral edema.

Subject 105-1201 had >3 times ULN for serum AST; subject discontinued prematurely because of sinusitis.

These subjects were not taking bosentan:

Subject 105-1201 had a history of hepatitis C virus infection, esophageal varices, and repair of esophageal varices. At baseline of Study LVGY, the subject had an elevated serum AST and ALT.

Subject 118-1854 had a history of hyperbilirubinemia, fatty liver, elevated serum enzymes, and alcohol abuse. At baseline of Study LVGY, the subject had an elevated serum AST and an elevated serum bilirubin.

Subject 601-6601 was a 69-year-old female with normal serum AST and bilirubin levels at baseline; ALT levels were slightly elevated. There was a transient increase in aminotransferases without an increase of bilirubin. Liver chemistry assessments were normal during the next two visits but slightly increased on Visit 8. The subject's bilirubin remained within normal limits at all times.

Subject 601-6616 had a history of hepatitis C virus infection and Gaucher's disease. At baseline of Study LVGY, the subject had an elevated serum AST/ALT and bilirubin.

7.1.8 Vital Signs

Study LVGU was a double blind, placebo controlled study in subjects with essential hypertension. Once daily doses of tadalafil up to 20 mg produced placebo subtracted seated blood pressure decreases of 5.3 mmHg diastolic and 3.6 mmHg systolic. Dyspepsia was reported by 10.5% of subjects receiving the 20 mg dose. The sponsor currently is not pursuing this indication.

There were few adverse events reported in LVGY indicative of blood pressure or heart rate change: palpitations (5 tadalafil 2.5 mg, 7 tadalafil 10 mg, 3 tadalafil 20 mg, 1 tadalafil 40 mg), bradycardia (1 tadalafil 40 mg), tachycardia (1 tadalafil 10 mg and 1 tadalafil 20 mg), hypotension (2 tadalafil 20 mg and 1 tadalafil 40 mg), blood pressure decreased (1 tadalafil 10 mg), blood pressure increased (1 tadalafil 2.5 mg and 1 tadalafil 20 mg), and syncope (1 tadalafil 2.5 mg, 2 tadalafil 10 mg, 2 tadalafil 20 mg).

7.1.9 Electrocardiograms (ECGs)

No new information about tadalafil and ECGs has been submitted.

7.1.10 Immunogenicity

No new information about tadalafil and immunogenicity has been submitted.

7.1.11 Human Carcinogenicity

No new information about tadalafil and human carcinogenicity has been submitted.

7.1.12 Special Safety Studies

No special safety studies have been submitted or contemplated.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No drug-dependence study in animals has been conducted.

There are no findings indicating that tadalafil causes physical or mental dependency.

7.1.14 Human Reproduction and Pregnancy Data

No new non human data available.

There was 1 pregnancy in Study LVGY (Subject 120-1952, subsequently enrolled in Study LVGX) and 1 additional pregnancy reported (Subject 113-1605, unconfirmed by pregnancy test) as of the interim database lock for Study LVGX.

Subject 120-1952 was discovered to be pregnant after receiving 2 doses of tadalafil 40 mg. She was discontinued from study drug and delivered at week 36. Both she and the baby were well at the time of interim database lock for Study LVGX.

Subject 113-1605 in study LVGX was not listed as pregnant because a blood or urine test was not performed. Because of the severity of PAH in this subject, a therapeutic abortion was performed without complications.

7.1.15 Assessment of Effect on Growth

Not evaluated.

7.1.16 Overdose Experience

No overt serious toxicity was observed when tadalafil, up to 500 mg, was administered as a single dose, or when tadalafil 100 mg was administered once daily for 3 weeks (see previous NDA). During the study, there were no reported serious adverse events and no changes in vital signs, laboratory values, and ECG findings.

In a study for the indication of ED (LVBG Study Report, previously submitted) in which tadalafil 10 to 100 mg (co-precipitate tablet formulation) was administered once daily for 3 weeks in male patients with mild and moderate ED. In the tadalafil 100 mg treatment group, serious adverse events (cardiac failure congestive and cholelithiasis) were reported in 2 subjects and 17 subjects discontinued the study because of adverse events. During the study, there were no reported clinically significant changes in vital signs, laboratory values, or ECG findings.

There are no reported events in humans receiving tadalafil at doses more than 500 mg by a single administration or more than 100 mg by repeated administration.

The clearance of tadalafil is not enhanced by renal dialysis.

7.1.17 Post marketing Experience

Tadalafil was first approved in Australia on October 15, 2002 for the treatment of ED. Since then it has been approved for the treatment of ED in 114 countries and is marketed in approximately 105 countries as of October 15, 2007. Only 1 tadalafil dose form, a filmcoated tablet in 4 strengths (2.5, 5, 10, and 20 mg) is available.

As of September 30, 2007, approximately patients worldwide have been exposed to tadalafil. b(4)

A total of 7 cases have been identified within the Lilly Safety System reporting pulmonary hypertension as the primary indication for use. Of these cases, 6 were reported or confirmed by a health care professional. The reported events included mania, physician prescribed overdose, QT prolongation, blood potassium abnormal, nausea, pain in the extremity, and burning sensation.

The sponsor conducted a retrospective analysis of the use of Cialis in men suffering from ED. After examining spontaneous adverse event reports and ECG data, the sponsor concluded that there is no causal link. They will continue to monitor such events. Thee sponsor continued to reports of eye disorders and sudden hearing loss. These two events are included in the WARNINGS AND PRECAUTIONS section of labeling.

7.2.3 Safety Update

This 4-Month Safety Update report for tadalafil provides safety information collected from PAH and non-PAH clinical studies between the NDA submission cut-off date (May 25, 2008) and the 4-Month Safety Update data cut-off date (September 26, 2008). The agreement with the sponsor stated that deaths and serious adverse events from Study H6D-MC-LVGX (Study LVGX) between the submission data cut-off date and the date of the pulmonary arterial hypertension (PAH) submission would be included. Also, for ongoing or recently completed non-PAH tadalafil once daily dosing studies, the sponsor provided tables of reported deaths and serious safety plus a table of descriptions for those studies.

The studies included in this review are:

- PAH studies: Study LVGX (safety and efficacy, ongoing) and Study H6D-MC-LVHU (Study LVHU, compassionate use, ongoing).
- Clinical pharmacology studies: Study H6D-EW-LVHN (Study LVHN BPH-LUTS, completed).

- Tadalafil once daily dose (all indications): Study H6D-MC-LVHG (Study LVHG, double-blind part is concluded; open-label part is ongoing), Study H6D-MC-LVHK (Study LVHK, concluded), H6D-MC-LVHT(concluded), and H6D-CR-S024 (Study S024) ongoing.

There were no newly initiated or completed PAH studies since the NDA submission. Other than Study S024, there were no other tadalafil once daily dosing studies (any non-PAH indication) initiated during the reporting time period. Study LVHN was concluded prior to the reporting time period and the CSR was completed during the reporting time period (approved August 11, 2008, submitted to IND 73,502). The safety results were not included in the original NDA submission, however, there were no reported serious adverse events or deaths in Study LVHN.

Study LVHG has 2 parts: a double blind part that was considered concluded during the reporting time period and an open-label part of the study (limited to 2 countries) that was ongoing during the reporting time period.

Details of the ongoing PAH trials are shown below.

Table SU.3. Tabular Listing of Ongoing Studies (from 26 May 2008 to 26 September 2008)

Study Type	Study Identifier	Key Objective(s)	Study Design	Enrollment	Key Inclusion Criteria	Study Drug(s)*	Treatment Duration	Primary Endpoint(s)
PAH Clinical Efficacy and Safety	H6D-MC-LVGX	<p>Part 1: <u>Primary:</u> To evaluate the long-term safety of tadalafil 20-mg and 40-mg once-daily in the treatment of patients with PAH.</p> <p><u>Secondary:</u> To determine the durability of efficacy of tadalafil.</p> <p>Part 2: To provide continued access to tadalafil for patients completing Part 1.</p>	<p>Part 1: Double-blind extension phase</p> <p>Part 2: Open-label phase</p>	<p>Part 1: 350 Subjects Males and Females</p> <p>Part 2: Based on enrollment from Part 1</p>	<p>Subjects who discontinue the placebo-controlled study (Study LVGY) due to clinical worsening of PAH and are on placebo, tadalafil 2.5 mg, 10 mg, or 20 mg or</p> <p>Subjects who complete Week 16 in the placebo-controlled study (Study LVGY) and have either no clinical worsening or clinical worsening at the Week 16 visit and are receiving placebo, tadalafil 2.5 mg, 10 mg, or 20 mg.</p> <p>Part 2: Completion of Part 1</p>	<p>Tadalafil 20 mg tablets</p> <p>Orally and QD</p> <p>Part 1: Tadalafil 20 mg or Tadalafil 40 mg</p> <p>Part 2: Tadalafil 40 mg</p>	<p>Part 1: 52 weeks</p> <p>Part 2: Indeterminate</p>	<p>TEAEs, SAEs, deaths, clinical laboratory values</p>

Summary of notable subjects: As of the data cut-off date, 28 subjects had a total of 41 new SAEs. One subject had prior SAE updated only and 2 subjects had new SAEs and prior SAEs updated. Six subjects died.

Table SU.3. Tabular Listing of Ongoing Studies (from 26 May 2008 to 25 September 2008) (Continued)

Study Type	Study Identifier	Key Objective(s)	Study Design	Enrollment	Key Inclusion Criteria	Study Drug(s)*	Treatment Duration	Primary Endpoint(s)
PAH Compassionate Use	H6D-MC-LVHU	Compassionate use requests for investigational use of tadalafil for PAH.	Not applicable	Not applicable	An unsolicited request has been received from a physician on behalf of his/her patient Have a diagnosis of symptomatic PAH (WHO functional Class II, III, or IV) Not be eligible to participate in any ongoing trial with tadalafil, unable to be transferred to a site of such a clinical trial, or have no availability of an ongoing clinical trial.	Tadalafil tablets Orally, single dose 2 x 20 mg (40 mg)	Not applicable	Not applicable

Summary of notable subjects: As of the data cut-off date, 1 subject had a new SAE and there were no deaths.

Since the cut off date for the NDA (May 25, 2008), no new subjects have been newly exposed to tadalafil in the ongoing PAH Studies LVGX or LVHU. There were no newly exposed subjects in ongoing non-PAH Study LVHG and there were 21 new subjects in Study S024 who received tadalafil. As this was not a significant increase in exposure amongst PAH subjects, a combined reanalysis of safety data was not performed.

Results

Overall, 32 subjects had 47 new or updated serious adverse events reported during the reporting time period. Six of the 32 subjects had previously reported serious adverse events that were updated:

- LVGX-0114-1659 Myocardial infarction (subject died),
- LVGX-0503-5701 circulatory collapse (subject died),
- LVGX-0114-1651 Cardiac Failure Congestive,
- LVGX-0805-7352 Diarrhoea,
- LVHK-0115-2518 Cellulitis,
- LVHU-0001-1-1 Myocardial infarction.

There were 4 new deaths during the reporting time period (all from extension study LVGX):

- LVGX-0302-4254 Cardiac Arrest
- LVGX-0113-1610 Death (80 year old female died after 473 days on drug)
- LVGX-0118-1853 Cardiac arrest (died after 556 days on drug)
- LVGX-0104-1152 Lobar pneumonia

New serious events that were reported by more than 1 subject in Study LVGX were cardiac arrest, chest pain, cardiac failure congestive, chest pain, and pulmonary hypertension. There was one report of hemoptysis (Subject LVGX-0906-8409).

There are 2 subjects in LVGX who reported life threatening cancers (colon and oropharyngeal stage III) during the update timeframe.

From the non-PAH tadalafil studies (all indications: Studies LVHG, LVHK, LVHN, LVHT, and S024), only 1 new subject (LVHG-0124-3417) had 1 serious adverse event (gastroesophageal reflux disease) that was new in LSS database during the reporting time period. There was 1 subject (LVHK-0115-2518) with an updated serious event (cellulitis). There were no reported deaths in the 5 non-PAH studies.

Safety update for Study LVGX (submitted January, 2009)

The sponsor submitted a brief synopsis of safety data from ongoing Study LVGX. The database cut off date for this report was November 13, 2008. It includes any additional reported deaths, serious adverse events, and discontinuations because of adverse events.

Deaths

No new deaths occurred between the 4-month safety update cut off date (September 26, 2008) and the database cut off date for the current update.

Serious adverse events

Eight subjects have reported new serious events. In all, 83 subjects in Study LVGX have reported at least one serious adverse event. Those events reported by more than two subjects include right ventricular failure (12), pulmonary hypertension (10), pneumonia (9), chest pain (5), anemia (3), non-cardiac chest pain (3), and peripheral edema (3).

Discontinuations because of adverse events

There has been one additional report of a discontinuation because of adverse events. In all, 30 subjects have discontinued from the study for this reason. Events leading to discontinuation that were reported by at least 2 subjects include PAH (4), right ventricular failure (4), sudden cardiac death (2).

Review of Study H6D-MC-LVGY

Title

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.

Objectives

The primary objective of this study was to evaluate the safety and efficacy of tadalafil 2.5 mg, 10 mg, 20 mg, and 40 mg once daily in the treatment of patients with PAH.

Study Design

This was a multicenter, randomized, double-blind, double-dummy, placebo-controlled study of tadalafil given orally to subjects with PAH. Subjects who met all eligibility criteria were stratified by PAH etiology, bosentan use, and baseline 6-minute walk distance (≤ 325 m and > 325 m). Subjects were randomized¹² 1:1:1:1:1 to receive either tadalafil 2.5 mg, 10 mg, 20 mg, 40 mg, or placebo once daily for 16 weeks. Those subjects completing the Week 16 visit were allowed to be considered for the extension trial. Those subjects not going into the extension trial had an additional study visit 2 weeks later (Week 18 visit).

Week 12 (trough drug levels): Subjects were instructed to take their study drug after the 6 minute walk test and blood samples for concentrations. The previous dose should have been taken the day before the study visit.

Primary efficacy endpoint: 6 minute walk (6-MW) distance change from baseline to end of treatment (week 16).

Primary Efficacy Analyses

The ITT population for the primary analysis included all subjects who were randomized to treatment and received at least 1 dose of study drug. 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 testing level of significance for the primary and secondary endpoints was 2-sided 0.01 and 2-sided 0.05, respectively. A step-down procedure was used to address the multiplicity issues when comparing each tadalafil dose with placebo on multiple endpoints. The endpoints were tested in this order: change in 6-MW distance (primary), change in WHO functional class, time to first occurrence of clinical worsening, and change in Borg dyspnea score. A 2-dimensional multiplicity adjustment algorithm began testing from tadalafil 40 mg compared with placebo on the primary endpoint. If this was statistically significant at the 2-sided level of significance at 0.01 then, (i) testing proceeded downward to the next lower dose on the primary endpoint tested at the 2-

¹² The randomization scheme was performed by a computerized interactive voice-response system (IVRS) at a central location for all sites. The IVRS system was used to balance the number of subjects receiving right heart catheterization for each treatment arm.

sided level of significance at 0.01, and (ii) testing proceeded to the next secondary endpoint tested at the 2-sided level of significant at 0.05.

The null hypothesis of no difference between each of the tadalafil treatment groups and placebo was tested. Primary and key secondary analyses based on continuous outcomes (that is, 6-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 as follows:

–For subjects who died or discontinued from the study due to clinical worsening (lung transplantation, atrial septostomy, worsening of WHO functional class, hospitalization due to worsening of PAH, or initiation of new PAH therapy), ranks were assigned as if the subject had the lowest possible outcome.

–For subjects who discontinued early due to treatment-related AEs in the absence of clinical worsening, a value of zero was imputed for the change from baseline in 6-MW distance (that is, no benefit from treatment) and ranked relative to the remainder of the data.

–For all other subjects, including those who completed the Week 16 visit but the visit was outside of the visit window or who discontinued early for any other reason, the most recent nonmissing postbaseline data were carried forward (last observation carried forward; LOCF).

Descriptive statistics were also calculated. Subjects who died or discontinued due to disease worsening had their data treated as missing in later scheduled visits with last available nonmissing value imputed (LOCF). Post hoc sensitivity analysis for the calculation of descriptive statistics was also done to mimic the ranking strategy in the primary analysis.

Since randomization was stratified by 3 factors (PAH etiology, use of bosentan, baseline 6-MW distance), the treatment difference compared to placebo was estimated using analysis of covariance (ANCOVA) with Type II sum of squares. This was considered more appropriate than the population mean. The ANCOVA model included effects for treatment group, centered baseline of 6-MW distance, PAH etiology, and bosentan use. Normality of the residuals was also tested. Additionally, the treatment difference compared to placebo and the corresponding 95% confidence intervals were estimated by Hodges-Lehmann method.

Secondary efficacy endpoints

1) improvement in WHO functional class (using the Cochran-Mantel-Haenszel test),
2) time to clinical worsening defined as any of the following:

- death,
- lung transplantation,
- atrial septostomy,
- hospitalization because of worsening PAH,

- initiation of new PAH therapy (prostacyclin or analog, endothelin receptor antagonist, PDE5 inhibitor), or
- worsening WHO functional class (using stratified permutation based log-rank test), and
- 3) change in Borg dyspnea score (using the same procedure as the primary endpoint).

Reviewer's comment: As the secondary endpoints are only to support the primary endpoint and not for additional indications, then it seems reasonable to use the 0.05 significance level for the study-wise type I error for the secondary endpoints, and the multiplicity adjustment procedure also seems reasonable, though it does not ensure a strong control of study-wise type I error rate.

Other endpoints were:

- Cardiopulmonary hemodynamic (includes mean pulmonary artery pressure, pulmonary vascular resistance, mean right atrial pressure, cardiac index, cardiac output, pulmonary capillary wedge pressure, mean arterial pressure, mixed venous oxygen saturation, systemic arterial oxygen saturation, systemic vascular resistance) changes from baseline to Week 16.
- Quality of Life, as measured by change in Short-Form-36v2 Health Survey (SF-36v2) and EuroQol scores from baseline to Week 16.

Additional efficacy objectives

Analyses for Quality of Life and cardiopulmonary hemodynamic parameters assessed using descriptive statistics, including confidence intervals and p-values, with available data.

Type of subject

Inclusion Criteria:

- ≥ 12 years of age (at screening).
- Body weight ≥ 40 kg (at screening).
- Currently have a diagnosis of PAH that is either (a) idiopathic, (b) related to collagen vascular disease, (c) related to anorexigen use, (d) related to HIV infection, (e) associated with an atrial septal defect, or (f) with surgical repair, of at least 1-year duration, of a congenital systemic-to-pulmonary shunt (e.g., ventricular septal defect, patent ductus arteriosus).
- Have a history of the diagnosis of PAH established by a resting mean pulmonary artery pressure ≥ 25 mm Hg, pulmonary artery wedge pressure ≤ 15 mm Hg, and pulmonary vascular resistance (PVR) ≥ 3 Wood units via right heart catheterization. In the event that a pulmonary artery wedge pressure is unable to be obtained during right heart catheterization, subjects with a left ventricular end diastolic pressure (LVEDP) < 15 mm Hg, with normal heart function, and absence of mitral stenosis on echocardiography, can be eligible for enrollment.
- If on bosentan, must be on a maintenance dose not greater than 125 mg twice daily for at least 12 weeks prior to screening and have a screening AST/ALT < 3

times the upper limit of normal.

- If on beraprost sodium (allowed for subjects only in Japan), must be on for at least 9 consecutive months before study entry, must be on a maintenance dose no greater than 180 µg per day, and must have no change in maintenance dose during the 12 weeks prior to screening.
- Have a chest radiograph within 6 months of screening that shows clear lung fields or no more than mild patchy (not diffuse) interstitial infiltrates.
- Have no evidence of significant parenchymal lung disease, as evidenced by pulmonary function tests within 6 months of screening showing total lung capacity $\geq 60\%$ predicted.
- Have a 6-minute walk test distance ≥ 150 and ≤ 450 meters at screening.
- Have World Health Organization (WHO) functional class I, II, III or IV status.
- A female subject of childbearing potential must have a negative serum pregnancy test at the screening visit and agree to use two medically reliable methods of contraception (e.g., barrier with either spermicide or hormonal contraception) until study completion.
- Written informed consent (and written assent for minors) will be obtained before any study procedure is performed.

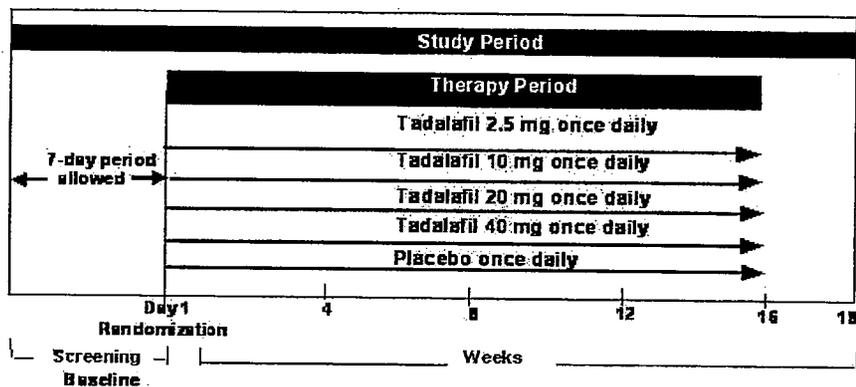
Exclusion Criteria:

- nursing or pregnant.
- Have pulmonary hypertension related to conditions other than specified above, including but not limited to chronic thromboembolic disease, portal pulmonary hypertension, or left-sided heart disease.
- For subjects with PAH associated with an atrial septal defect, resting arterial oxygen saturation (SaO₂) $< 88\%$ on room air at screening.
- History of left-sided heart disease, including any of the following:
 - clinically significant aortic or mitral valve disease (i.e., aortic stenosis, aortic insufficiency, mitral stenosis, moderate or greater mitral regurgitation);
 - pericardial constriction;
 - restrictive or congestive cardiomyopathy;
 - left ventricular ejection fraction $< 40\%$ by multigated radionuclide angiogram (MUGA), angiography, or echocardiography;
 - left ventricular shortening fraction $< 22\%$ by echocardiography;
 - life-threatening cardiac arrhythmias;
 - symptomatic coronary artery disease within 5 years of study entry.
- History of atrial septostomy within 3 months before study entry.
- Have severe hepatic impairment, Child-Pugh Grade C.
- Have severe renal insufficiency.
- Have a systolic blood pressure >160 mm Hg or < 90 mm Hg, or diastolic blood pressure >100 mm Hg or < 50 mm Hg at screening.
- Have a history of angina pectoris or other condition that was treated with

long- or short-acting nitrates within 12 weeks before administration of study drug.

- Have a musculoskeletal disorder (e.g. arthritis, artificial leg, etc.) or any other disease besides pulmonary arterial hypertension that may significantly limit ambulation.
- Have any new long-term treatment for pulmonary arterial hypertension added within 4 weeks before administration of study drug.
- Have any therapy with a prostacyclin or analogue, L-arginine, phosphodiesterase inhibitor, or investigational drug within 4 weeks before administration of study drug. An exception is allowed in Japan for subjects who have been treated with beraprost sodium.
- Have any chronic PAH medication except for anticoagulants discontinued within 4 weeks prior to administration of study drug.
- Current treatment with antiretroviral therapy (protease inhibitor), systemic ketoconazole, or systemic itraconazole.
- Are investigator site personnel directly affiliated with the study, or the immediate family of investigator site personnel directly affiliated with the study. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
- Are employed by Lilly or ICOS (that is, employees, temporary contract workers, or designees responsible for the conduct of the study). Immediate family of Lilly or ICOS employees may participate in Lilly ICOS LLC-sponsored clinical trials, but are not permitted to participate at a Lilly or ICOS facility. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

Study Procedures



Screening and baseline evaluations occurred within a 7-day period. Day 1 was defined as the day of randomization.

Test	When performed
Efficacy	
Six-minute walk distance with Borg dyspnea score	screening/baseline and Week 4, 8, 12, and 16. Trough values only at week 12.
WHO functional class status	screening/baseline and Week 4, 8, 12, and 16

Quality of Life as measured by the Short-Form-36v2 Health Survey (SF-36v2)	baseline, Week 8, and Week 16.
EuroQol Questionnaire	baseline, Week 8, and Week 16.
Cardiopulmonary hemodynamics, obtained by right heart catheterization	baseline and Week 16 visits in a subset of subjects (approximately 85)
Safety	
vital sign evaluations every 30 minutes for 2 hours	following first dose of study drug
Physical (including ophthalmologic) exams and ECGs	screening or baseline, and Week 16
trough serum digoxin concentrations for subjects taking digoxin	baseline and Week 1 and 4 visits.
international normalized ratio values for subjects taking warfarin	week 1 in addition to the values collected with the coagulation panel for all trial subjects at baseline and Weeks 4, 8, 12, and 16
liver function values for subjects taking bosentan	week 2 visit in addition to the values collected with the serum chemistry panel for all trial subjects at baseline and Weeks 4, 8, 12, and 16.
plasma tadalafil concentrations for population analyses	week 4, 8, 12, and 16

Subjects who discontinued the study at any time and did not enter the extension trial were to have WHO functional classification and adverse events collected by telephone or site visit approximately 16 weeks following their randomization.

Planned sample size: Approximately 400 subjects with 80 subjects/treatment arm. Power: 90% at an α -level of 0.01 (2=sided). A step-down procedure will be used to adjust for multiple comparisons.

Changes in the Conduct of the Study

The original protocol was approved by the Sponsor on 05 April 2005 and was amended 6 times.

- 1) Amendment 1 (approved 03 May 2005) was administrative in nature and released prior to subject enrollment to the study.
- 2) Amendment 2 (approved 10 May 2005) was a result of changes requested by a medical expert in PAH, and included adding an upper limit of systolic and diastolic blood pressures at screening in addition to other minor clarifications. Amendment 2 was released on 10 May 2005, prior to any subject enrollment.
- 3) Amendment 3 (approved 11 May 2005) added the EuroQoL Questionnaire for capture of QoL measures in the study. Amendment 3 was released on 11 May 2005, prior to any subject enrollment.
- 4) Amendment 4 (approved 26 July 2005) was initiated because of a request from the FDA the inclusion of ophthalmologic exams. In addition, as part of Amendment 4, the number of study sites planned was increased to 80 (from 60).
- 5) Substantive changes were incorporated into Amendment 5 (approved 15 May 2006), which involved amending the inclusion/exclusion criteria as follows:
 - included subjects with PAH related to HIV infection;
 - expanded inclusion criterion for established diagnosis of PAH to include LVEDP for subjects in which PCWP was unobtainable during right heart

catheterization;

–changed inclusion criterion regarding the daily maintenance dose for subjects receiving bosentan therapy;

-changed exclusion criterion for symptomatic coronary artery disease to specify disease that occurred within 5 years of study entry;

6)Amendment 6 was included to allow Japan to participate.

Results

There was a total of 457 subjects entered into the study from Western Europe, North America, Japan, and UK. North America enrolled the majority of subjects (60%). Of this, there were 406 randomized to a treatment group, 405 received at least one dose of study drug. The number of subjects randomized per treatment group ranged from 79 to 82.

Type of Subject

Demographics, duration of PAH, PAH etiology, and characteristics of PAH at baseline are shown by treatment group in the tables below.

Demographics

	Placebo	tadalafil			
		2.5 mg	10 mg	20 mg	40 mg
Randomized (#)	82	82	81	82	79
Mean age (y)	55	54	54	53	53
>75 y (%)	13	7	9	6	6
Female (%)	79	78	84	76	75
White (%)	88	79	80	74	81
Mean weight (kg)	77	76	74	76	74

The study subjects were approximately 54 years of age, predominantly female and predominantly white. The percentage of subjects at least 75 years of age was greatest for placebo (13%) compared to tadalafil groups (range 6%-9%). Mean weight was around 75 kgs. The groups were fairly well balanced.

PAH: Duration of disease (% of subjects)

	Placebo	tadalafil			
		2.5 mg	10 mg	20 mg	40 mg
years					
>0-<2y	60	50	59	56	52
>2 -<4y	14	20	28	15	18
>4 y	24	30	14	29	30

Most subjects had their disease less than 4 years. The treatment groups are well balanced.

PAH: etiology (% of subjects)

	Placebo	tadalafil			
		2.5 mg	10 mg	20 mg	40 mg
Idiopathic	66	55	65	61	58
Related to collagen vascular disease	20	20	29	26	24
Atrial septal defect	11	9	5	5	10
Anorexigen use	2	6	1	5	5
Surgical repair >1 yr	1	11	0	4	3

The etiology of PAH was defined as idiopathic for the majority of the subjects with “related to collagen vascular disease” the second most common. The groups were reasonably well balanced.

PAH: disease characteristics

	Placebo	tadalafil			
		2.5 mg	10 mg	20 mg	40 mg
taking bosentan (%)	55	52	51	55	53
Mean baseline 6 min walk (m)	343	347	338	337	352
WHO functional class (%)					
I	1	1	0	0	3
II	28	35	30	34	33
III	68	60	68	66	65
IV	2	4	3	0	0
Mean Borg dyspnea score	4	4	4	4	4

More than half of subjects were taking bosentan, the mean 6-minute walk distance ranged from 343 to 352 m, and most were WHO functional class II or III. The treatment groups were well balanced.

Concomitant medications

Common concomitant medications (reported by at least 50 tadalafil subjects) included acetylsalicylic acid, furosemide, levothyroxine, oxygen, paracetamol, potassium, and spironolactone.

Subject disposition

The numbers of subjects with various trial outcomes are shown below by treatment group.

Number and (%) of subjects

	Placebo	tadalafil			
		2.5 mg	10 mg	20 mg	40 mg
randomized	82	82	81	82	79
completed week 16	69 (84)	64 (78)	71 (89)	66 (80)	71 (90)
early dc'd	13 (16)	18 (22)	9 (11)	16 (20)	8 (10)
died	1 (1)	0	1 (1)	0	0
dc'd for adverse event	12 (15)	13 (16)	6 (8)	9 (11)	7 (9)
dc'd because of invest decision	0	0	0	3	0
Lost to follow up	0	0	1 (1)	0	0
dc'd because of protocol not met	0	0	0	2 (2)	0
dc'd because of needing other PAH meds	0	0	0	2 (2)	1 (1)
withdrew consent	0	5 (6)	1 (1)	0	0

Table 10.1

A somewhat higher percentage of tadalafil 40 mg group (90%) completed week 16 compared to the other groups. The tadalafil 2.5 mg group had the lowest percentage of completers (78%).

There were 2 deaths (placebo and 10 mg).

The majority of premature drop outs were reported to have occurred because of adverse event(s). The placebo group had the greatest percentage of drop outs for this reason (15%) and tadalafil 10 mg had the lowest (8%).

The reasons given for those who withdrew because of adverse events are shown below.

Number and (percent) of subjects

	Placebo	tadalafil			
		2.5 mg	10 mg	20 mg	40 mg
Total randomized	82	82	81	82	79
Total dc'd for AE	12 (15)	13 (16)	6 (8)	9 (11)	7 (9)
Hosp. for worsening PAH	1 (1)	1 (1)	1 (1)	0	1 (1)
Worsening of WHO functional class	7 (9)	7 (9)	2 (3)	4 (5)	3 (4)
Other AE	4 (5)	5 (6)	3 (4)	5 (6)	3 (4)

There were 4 hospitalizations for worsening PAH, evenly distributed among the treatment groups (except for tadalafil 20 mg which had none). The highest percentages of subjects with worsening WHO functional class were in the placebo and tadalafil 2.5 mg groups.

Drop outs for “other adverse events” were almost evenly distributed across treatment groups.

Efficacy results

The primary efficacy endpoint was the 6 min walk test.

The total number of subjects excluded from the primary endpoint analysis was 13 (3 placebo, 3 tadalafil 2.5 mg, 2 tadalafil 10 mg, 2 tadalafil 20 mg, and 3 tadalafil 40 mg). The results of the walk test are shown below.

6 Min walk (m)

	Placebo n=79	Tadalafil			
		2.5 mg n=79	10 mg n=78	20 mg n=80	40 mg n=76
Mean baseline walk distance (SD)	347.49 (81.18)	346.53 (71.60)	340.01 (72.80)	338.26 (74.45)	352.67 (78.75)
Mean change from baseline at week 16 (SD)	9.21 (59.96)	21.79 (60.83)	28.6 (62.17)	36.23 (47.53)	41.14 (49.39)
95% CI	-4.22, 22.65	8.17, 35.42	14.58, 42.61	25.65, 46.81	29.85, 52.42
Placebo subtracted means*	-	10	16	22	26
P value+	-	0.402	0.0466	0.0278	0.0004

^95% CI is calculated based on t distribution

+Permutation test stratified by PAH etiology, bosentan use, and baseline 6 min walk distance (≤ 325 m and >325 m) on rank compared to placebo.

*Hodges-Lehmann method

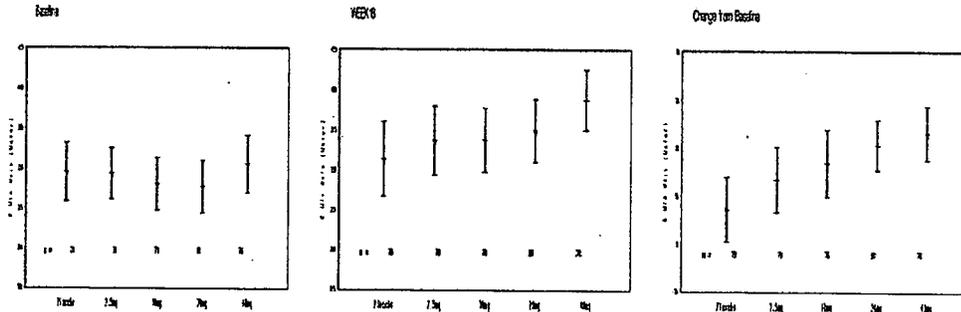
Table LVGY.11.4

The mean 6 minute walk distance at baseline was approximately 345 m with the range from 338.26m (20 mg dose) to 352.67m (40 mg dose).

Mean increase in 6 minute walk test from baseline at endpoint was the smallest for placebo (9 m). The mean change from baseline at endpoint for the tadalafil groups grew larger with larger doses. The placebo-subtracted effect was 10 m, 16 m, 22 m and 26 m for tadalafil 2.5 mg, 10 mg, 20 mg, and 40 mg, respectively.

The figures below show the 6 minute walk tests at baseline, week 16, and change from baseline by treatment group.

6-minute Walk Distance (meters) by Visit, Last Non-missing Observation
in Treatment Period Carried Forward
Summary and Analysis by Randomized Study Treatment Group
All ITT Subjects (N=405)
Study H6D-MC-LVGY



Program Location: RMP.H6DSLVCY.SASPGM(GFN08CY)
Output Location: RMP.H6DC.LVGY(GFN08CYD)
Data Set Location: RMP.SAS.H6DS.L.MCLVGY.ADS

LVGY.11.1. 6-MW distance at baseline, week 16, and change from baseline for all ITT subjects using LOCF.

Tests of significance for the primary endpoint was based upon a rank transformation. Each tadalafil treatment group was compared to placebo using a permutation test stratified by PAH etiology, bosentan use, and baseline 6 minute walk distance. A step down procedure, starting with tadalafil 40 mg group, was used to take into account the 4 comparisons with placebo. The significance level for the study since it is the only one used to demonstrate efficacy was 0.01 (2-sided).

Only the 40 mg dose was significantly better than placebo ($p=0.0004$) in prolonging the walk distance at week 16. Tadalafil 20 mg could be supported as the minimum effective dose, although it did not meet the prespecified significance level of 0.01 ($p=0.0278$).

Doses above 40 mg should be examined in future studies.

Following the step-down procedure, no primary efficacy statistical testing for lower tadalafil doses should be performed. For the secondary endpoints, statistical testing can be performed only for tadalafil 40 mg group, since only this group was statistically significantly superior to placebo relative to the primary endpoint. In this review, all secondary endpoints for all doses are presented only to allow complete and robust assessment of the study.

Exercise testing at other visits

The 6 minute walk test was performed at weeks 4, 8, and 12 as well as at week 16. The testing at week 12 was conducted at the “trough drug concentration”. The results for all weeks are shown below only for placebo and tadalafil 40 mg. The table showing the results for the lower doses and figures are in the appendix 1.

	Placebo n=79	tadalafil 40 mg n=76
Mean baseline walk distance (SD)	347.49 (81.18)	352.67(78.75)
# of subjects evaluated at week 4	79	72
Mean change from baseline at week 4 (SD)	10.47 (51.44)	20.03 (41.36)
Treatment effect	-	10
# of subjects evaluated at week 8	79	76
Mean change from baseline at week 8 (SD)	13.04 (48.79)	28.91 (45.74)
Treatment effect	-	16
# of subjects evaluated at week 12	79	76
Mean change from baseline at week 12 (SD)	10.14 (55.49)	36.25 (53.00)
Treatment effect	-	26
# of subjects evaluated at week 16	79	76
Mean change from baseline at week 16 (SD)	9.21 (59.96)	41.14 (49.39)
Treatment effect	-	32

LVGY 14.8

The test at week 12 was the “trough effect” (the subject performed the walk test prior to taking that day’s dose) showed a placebo subtracted 26 m improvement over baseline.

Compared to the previous visit, the walk distance for tadalafil 40 mg group increased by 6-10 m.

Subgroups

The sub groups of particular interest include bosentan use, age, gender, etiology of disease. The results for doses other than tadalafil 40 mg are shown in appendix 2.

Bosentan use

A total of 216 subjects (53%) were taking concomitant bosentan. (Subjects were stratified at the time of randomization according to whether or not they were taking bosentan.)

Baseline characteristics of the placebo and tadalafil groups, those with and those without bosentan, are shown in the table below.

	No bosentan		bosentan	
	Placebo	tadalafil 40 mg	Placebo	tadalafil 40 mg
Randomized (#)	37	37	45	42
Mean age (y)	59	55	52	50
>75 y (%)	14	14	13	0
Female (%)	81	70	78	79
White (%)	92	78	84	83
Mean weight (kg)	78	73	76	75
Duration of pah 0-<4 yrs (%)	84	78	69	62
Mean baseline walk test (m)	337	342	349	361
WHO functional class III (%)	68	73	69	57
Mean baseline Borg scale	4.6	4.0	3.7	4.11

There were a few small differences between the groups of subjects. Compared to subjects not on bosentan, the subjects taking bosentan were a little younger, and more likely to have had their PAH longer than 4 years. Baseline walk distance was somewhat longer for the subjects on bosentan.

In the group taking bosentan, those randomized to tadalafil 40 mg had a slightly longer baseline walk test (361 m) compared to those randomized to placebo (349 m).

The results of the 6 minute walk test, grouped by bosentan use, are shown below for the placebo and tadalafil 40 mg subjects.

6 min walk: Mean change from baseline at week 16 (m)

placebo		Tad 40 mg	
yes+ n=44	no^ n=35	yes+ n=39	no^ n=37
18.0	-6.0	40.7	38.4
Trx effect (Ancova model)		22.7#	44.3***

+Taking concomitant bosentan

^not taking bosentan

#p= 0.076 for bosentan plus placebo compared to bosentan plus tadalafil.

***p=0.0006 for placebo compared to tadalafil.

Those subjects in the tadalafil 40 mg group who were not taking bosentan walked more than twice as long compared to those taking bosentan.

Age

The table below shows the outcome of the 6 minute walk test for those subjects < 54 years old compared to those > 54 years old for the placebo and 40 mg dose.

6 min walk: Mean change from baseline at week 16 (m)

placebo		Tad 40 mg	
<54 yrs n=40	>54yrs n=39	<54yrs n=41	>54yrs n=35
17	1	50	31
Trx effect		33	30

LVGY.11.11

As expected, the younger subjects walked longer at baseline compared to the older subjects. The placebo subtracted walk distances mean change from baseline at week 16 were similar for both age groups.

Gender

6 min walk: Mean change from baseline at week 16 (m)

placebo		Tad 40 mg	
F n=62	M n=17	F n=57	M n=19
8	14	42	40
Trx effect		34	26

LVGY.11.11

There were 3.5 times as many females as males. The increase in the treatment effect was similar for the females and males.

Baseline walk test

The subjects were grouped according to baseline 6 min walk distance (>325 m versus ≤325 m).

6 min walk: Mean change from baseline at week 16 (m)

placebo		Tad 40 mg	
>325 n=51	≤325 n=28	>325 n=51	≤325 n=25
8	12	33	57
Trx effect		25	45

At baseline, approximately twice the number of subjects walked > 325 m compared to those who walked ≤ 325 m.

In the tadalafil 40 mg group, those subjects who walked ≤ 325 m at baseline had a greater increase in walk distance at endpoint compared to those with baseline > 325 m.

Secondary Endpoints

Following the step-down procedure, statistical analysis of the secondary endpoints can be only evaluated for tadalafil 40 mg, since only tadalafil 40 mg had a statistically significant improvement on the primary endpoint. All secondary endpoints for all doses are only presented to allow complete and robust clinical assessment of the study information.

The key secondary

efficacy endpoints are to be tested in order as follows:

- change from baseline to end of treatment in WHO functional class,
- time to clinical worsening, and
- change from baseline to end of treatment in Borg dyspnea score.

Other efficacy endpoints included hemodynamic parameters obtained in a subset of patients by right heart catheterization and QoL parameters (SF-36v2 and EuroQoL).

WHO Functional Class

The WHO functional class at baseline, week 16, and change from baseline at week 16 for the study subjects are shown below by treatment group.

Number of subjects: baseline

WHO functional class	Placebo n=82	Tadalafil			
		2.5 mg n=82	10 mg n=80	20 mg n=82	40 mg n=79
Class I	1	1	0	0	2
Class II	23	29	24	28	26
Class III	56	49	54	54	51

Class IV	2	3	2	0	0
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Most subjects were WHO functional class II and III at baseline. There was fairly even distribution among the treatment groups.

Number of subjects: week 16

WHO functional class	Placebo n=82	Tadalafil			
		2.5 mg n=82	10 mg n=80	20 mg n=82	40 mg n=79
Class I	2	4	1	7	5
Class II	32	34	36	41	38
Class III	34	27	31	20	28
Class IV	1	2	3	1	1
Unknown+	13	15	9	13	7

+subjects with no week 16 data are considered to have worsened from baseline in analysis.

Number and (percent) of subjects: Change from baseline at week 16

WHO functional class	Placebo n=82	Tadalafil			
		2.5 mg n=82	10 mg n=80	20 mg n=82	40 mg n=79
No change	52 (63)	43 (52)	50 (63)	37 (45)	53 (67)
worsen	13 (16)	18 (22)	11 (14)	15 (18)	8 (10)
Improved	17 (21)	21 (26)	19 (24)	30 (37)	18 (23)
P value+		0.97	0.58	0.17	0.36

+Cochran-Mantel-Haenszel test stratified by PAH etiology, bosentan use, and baseline 6-minute walk distance compared to placebo.

The majority of subjects had no change in their WHO functional class after 16 weeks of treatment¹³. There were no statistically significant differences between any tadalafil treatment group compared to placebo in incidences of WHO functional class improvement, no change, or worsening. However, tadalafil 40 mg group had a lower incidence of worsening (10%) compared to placebo (16%) and the other active treatment groups.

As tadalafil 40 mg group was not statistically significantly better than placebo (p=0.36) relative to WHO functional class, no statistical testing of other secondary endpoints should be performed. We present results for all secondary endpoints and all doses only to allow complete and robust assessment of the study.

Clinical worsening

Clinical worsening was defined in the study protocol as any of the following: death, lung transplantation, atrial septostomy, hospitalization because of worsening PAH, initiation of new PAH therapy (prostacyclin or analog, endothelin receptor antagonist, PDE5 inhibitor), or worsening WHO functional class.

The numbers of subjects who met one of these endpoints during the trial are shown below by treatment group.

¹³ At week 16, there is a large number of subjects without WHO functional class data

Number and (percent) of subjects

	Placebo n=82	Tadalafil			
		2.5 mg n=82	10 mg n=80	20 mg n=82	40 mg n=79
Total with clinical worsening	13 (16)	10 (12)	7 (9)	8 (10)	4 (5)
death	1	0	1	0	0
Hosp. for worsening PAH	2	2	3	0	1
New PAH rx	0	1	0	2	1
Worsening WHO class	11	10	6	6	3

Tadalafil 40 mg had fewer subjects who reported clinical worsening compared to the other treatment groups. This was primarily the result of fewer subjects reporting worsening of WHO functional class.

The mean number of days to clinical worsening for placebo and tadalafil 2.5, 10, 20, and 40 mg were 101, 103, 106, 103, and 106, respectively. The Kaplan-Meier curves for time to clinical worsening are shown below.

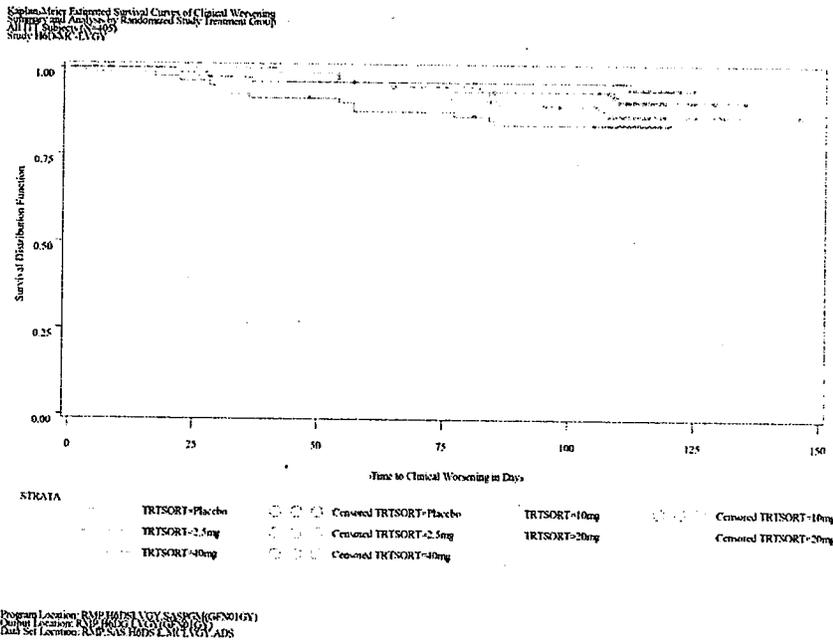


Figure LVGY.11.3. Kaplan-Meier survival curves for time to clinical worsening.

Borg dyspnea score

The Borg dyspnea score with walk test was obtained throughout the trial. The table below shows the mean baseline, mean endpoint, and change from baseline at endpoint and p-values by treatment group.

Borg score

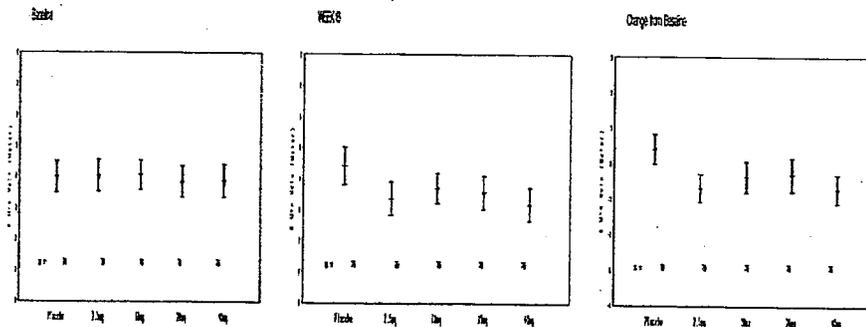
score	Placebo n=79	Tadalafil			
		2.5 mg n=79	10 mg n=78	20 mg n=78	40 mg n=76
Mean baseline	4.01	4.05	4.07	3.86	3.89
Mean endpoint	4.41	3.37	3.71	3.56	3.19
Change from baseline	0.40	-0.68	-0.36	-0.29	-0.70
p-value†	-	0.01	0.15	0.16	0.07

†primary analysis: permutation test stratified by PAH etiology, bosentan use, and baseline 6-minute walk distance on rank compare to placebo

The mean scores at baseline ranged from 3.86 to 4.07. At endpoint, all treatment groups, except placebo, had an improvement in the score. The tadalafil 40 mg group had the largest numeric change from baseline followed by the 2.5 mg group.

The results are shown in the figures below, by treatment group.

Borg Dyspnea Score by Visit, Last Non-missing Observation
in Treatment Period Carried Forward
Summary and Analysis by Randomized Study Treatment Group
All ITT Subjects (N=405)
Study H6D-MC-LVGY



Program Location: RWP H6D LVGY SASPCN(GFN10GY)
Output Location: RWP H6D LVGY(GFN10GYD)
Data Set Location: RWP SAS.H6D5.L.MC.LVGY.ADS

Figure LVGY.11.4. Borg dyspnea scores at baseline, week 16, and change from baseline for all ITT subjects using LOCF.

Cardiopulmonary hemodynamics

There were 93 subjects who participated in the cardiopulmonary hemodynamic substudy. There were statistically significant ($p < 0.05$) changes from baseline for the various parameters for all tadalafil groups but not the placebo group. The tadalafil 40 mg group showed improvements from baseline in mPAP, PVR, CI, and CO. The tables showing results for all treatment groups are in appendix 3.

Health outcomes/Quality of life evaluations

The SF-36v2 Health Survey evaluates 8 domains (physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, and mental health). Tadalafil seemed to improve most of these domains with the most improved scores displayed in the 40 mg dose. See appendix 4.

Improvements in the tadalafil groups were also shown in the EuroQoL Questionnaire which consists of 5 questions (mobility, self care, usual activities, pain/discomfort, anxiety/depression) as well as a visual analog scale to rate global health related QoL. Again, tadalafil 40 mg group displayed the most improvement.

Safety

Adverse events were to be collected through the Study Week 16 visit for subjects entering the extension study. Subjects completing the Week 16 study visit but not entering the extension trial were to have adverse events collected through their Week 18 visit. Subjects who discontinued the study at any time and did not enter the extension trial were to have WHO functional classification and adverse events collected by telephone or site visit approximately 16 weeks following their randomization.

Duration of exposure

Mean numbers of days on placebo and tadalafil 40 mg were 103 and 108, respectively.

Serious safety

Death

There were 3 reported deaths. These subjects are discussed below.

Deaths

ID/drug/dose	Days on drug	Cause of death
138 2854/tad/10 mg	109	Sudden death
912 8701/tad/20 mg	14	Hematophagic histiocytosis
128 2362/placebo/na	53	Pulmonary hypertension

Subject 138 2854, a 73 year old female with a medical history of Sjogren's scleroderma, Raynaud's, headaches, anxiety, depression, retinal inflammation,

seasonal allergies, sinus congestion, hiatal hernia, peptic ulcer, diverticulitis, irritable bowel syndrome, esophageal stricture. She was concomitantly receiving alprazolam, escitalopram, esomeprazole, prednisolone, triamcinolone, loperamide, and fexofenadine.

About 3 months after start of study drug, the subject presented with facial drooping, facial spasms and slurred speech. Bell's Palsy was diagnosed. After 15 weeks of being on study drug, the patient's daughter reported that the subject awakened complaining of a severe headache and intense body flushing. She became comatose and unresponsive (study day 109). Emergency personnel was unable to revive the patient. No autopsy was performed, and the cause of death was listed as sudden death (cause unknown).

Subject 912 8701 This was a 28-year old female who developed PAH secondary to systemic lupus erythematosus and Sjogren's syndrome. Her PAH was severe but controlled and stabilized by medication therapy with steroids. She was also suffering from osteoporosis and bilateral osteonecrosis of the femoral head.

Subject developed a headache one day after starting study drug. Shortly thereafter, she reported eyelid edema and eyelid pain. No abnormality was found and cyanocobalamin eye drops was prescribed. About one week after starting study drug the subject reported malaise. She became febrile and reported to the hospital with anorexia and malaise. CAT scan findings revealed pleural effusion. WBC and bacteria were noted in urine culture. Antibiotics were started and study drug was stopped. She was suspected to have developed TTP and hemophagocytic syndrome¹⁴ (HPS) and started therapy with methylprednisolone and hydrocortisone. Her health continued to decline and she was sent to the ICU with difficulty breathing, pleural effusion, decreasing blood pressure, a bleeding tendency and drop in platelet count. Bone marrow aspiration showed hemophagocytosis in some part, and so HPS associated with SLE was suspected. The subject died three days after discontinuing the study drug.

The autopsy revealed hemorrhagic lesions in various tissues and signs of steroid treatment. The cause of the death was considered to be the underlying pulmonary hypertension and cardiac failure. Although the biopsy revealed no hemophagocytosis, significant hemophagocytosis had been found in bone marrow when she was admitted to the hospital.

The third death occurred in a subject randomized to placebo.

Serious adverse events

The numbers of subjects reporting at least one serious adverse event are shown below by treatment group.

¹⁴ Hematophagic histiocytosis generally occurs in patients who develop infections in the setting of preexisting immunologic abnormalities or neoplasms. Viral infections are most commonly involved, but virtually any other infectious agent can precipitate this syndrome.

Serious adverse event reports: no. of subjects and (percent)

Placebo n=82	tadalafil			
	2.5 mg n=82	10 mg n=80	20 mg n=82	40 mg n=79
12 (15)	14 (17)	10 (13)	11 (13)	7 (9)

The treatment group with the highest percentage of serious adverse events is tadalafil 2.5 mg (17%) followed by placebo (15%). Tadalafil 40 mg has the lowest (9%).

Serious adverse events reported by at least 2 tadalafil subjects are shown below.

No. and (percent) of subjects

Serious event	Placebo n=82	tadalafil			
		2.5 mg n=82	10 mg n=80	20 mg n=82	40 mg n=79
Pulmonary hypertension	1 (1)	4 (5)	3 (4)	0	2 (3)
R ventricular failure	1 (1)	2 (2)	2 (3)	1 (1)	0
Anemia	0	2 (2)	0	1 (1)	0
dyspnea	0	1 (1)	1 (1)	1 (1)	0
URI	0	1 (1)	0	1 (1)	0

These serious adverse events are expected in this population.

Discontinuations because of adverse events

Discontinuations because of adverse event: no. of subjects and (percent)

Placebo n=82	Tadalafil			
	2.5 mg n=82	10 mg n=80	20 mg n=82	40 mg n=79
13 (16)	13 (16)	7 (9)	9 (11)	7 (9)

The 2 drug groups with the highest percentage of discontinuations for adverse events were placebo and tadalafil 2.5 mg (both 16%).

Adverse events leading to discontinuations by at least 2 tadalafil subjects are shown below.

No. and (percent) of subjects

event	Placebo n=82	tadalafil			
		2.5 mg n=82	10 mg n=80	20 mg n=82	40 mg n=79
Pulmonary hypertension	7 (8)	4 (5)	2 (3)	4 (5)	3 (4)
Back pain	0	0	1 (1)	0	1 (1)
Dyspnea	1 (1)	2 (2)	0	0	0
R ventricular failure	0	1 (1)	1 (1)	0	0

Other events leading to discontinuation included drug hypersensitivity (tadalafil 40 mg) and pregnancy (tadalafil 40 mg) resulting in a normal birth.

All adverse events

The adverse events reported by at least five subjects randomized to tadalafil 40 mg and reported by fewer subjects randomized to placebo are shown below by treatment group.

Adverse event reporting: no. and (percent) of subjects

event	Placebo n=82	tadalafil			
		2.5 mg n=82	10 mg n=80	20 mg n=82	40 mg n=79
Any event	65 (79)	72 (88)	72 (90)	69 (84)	75 (95)
Headache	12 (15)	15 (18)	30 (38)	26 (32)	33 (42)
myalgia	3 (4)	2 (2)	3 (4)	7 (9)	11 (14)
Flushing	2 (2)	3 (4)	5 (6)	5 (6)	10 (13)
Nasopharyngitis	6 (7)	4 (5)	6 (8)	2 (2)	10 (13)
Diarrhea	8 (10)	9 (11)	9 (11)	6 (7)	9 (11)
nausea	5 (6)	6 (7)	7 (9)	8 (10)	9 (11)
Pain in extremity	2 (2)	3 (4)	4 (5)	4 (5)	9 (11)
Back pain	5 (6)	5 (6)	5 (6)	10 (12)	8 (10)
Dyspepsia	2 (2)	4 (5)	2 (3)	11 (13)	8 (10)
Nasal congestion	1 (1)	3 (4)	3 (4)	0	7 (9)
Dyspnea	3 (4)	8 (10)	4 (5)	4 (5)	5 (6)
Chest pain	1 (1)	4 (5)	1 (3)	5 (6)	5 (6)
Vomiting	1 (1)	2 (2)	2 (3)	6 (7)	5 (6)
Fatigue	3 (4)	4 (5)	1 (1)	4 (5)	5 (6)

LVGY.12.3

Adverse events most commonly reported by the tadalafil 40 mg group include headache, myalgia, flushing, and nasopharyngitis (placebo subtracted incidence rates were 27%, 10%, 11%, and 6%, respectively).

Laboratory evaluations

Discontinuations for abnormal lab value

The following abnormal lab values led to subject withdrawal: liver function test (tadalafil 20 mg), increased creatinine clearance (tadalafil 2.5 mg), and neutropenia¹⁵ (tadalafil 10 mg).

There were few and scattered numbers of subjects with >3 times the upper limit of normal for ALT (2 placebo, and one each tadalafil 2.5 mg, tadalafil 10 mg, tadalafil 20 mg) or for AST (2 placebo, and one each tadalafil 2.5 mg, tadalafil 10 mg, tadalafil 20 mg, and tadalafil 40 mg. Liver enzyme elevations >5 times the ULN for serum ALT included one each placebo, tadalafil 2.5 mg, and tadalafil 10 mg; for serum AST there were 2 placebo and one tadalafil 2.5 mg.

¹⁵ Subject 603 6702 discontinued for neutropenia (neutrophils thousands/microliter visit 2: 1.9 and visit 6: 0.9; leucocyte count fell from 4.14 to 2.96).

There were low numbers of subjects in all treatment groups with platelet counts >100 GI/L at baseline and at any post baseline visit:

<100 GI/L (four placebo, one tadalafil 2.5 mg, and two tadalafil 40 mg),

<75 GI/L (placebo),

<50 GI/L (placebo), or

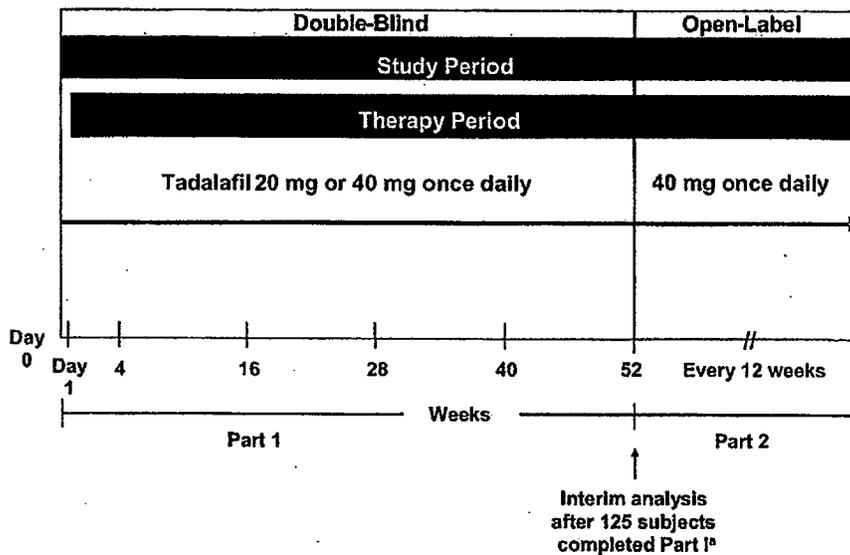
<20 GI/L (placebo).

There was one report of serious hypokalemia (tadalafil 20 mg) and one report of serious hematocrit/hemoglobin decrease (tadalafil 2.5 mg).

Review of study H6D-MC-LVGX

This is an interim review of the ongoing study H6D-MC-LVGX, an extension of study LVGY evaluating the safety of tadalafil 20 and 40 mg once daily in the treatment of PAH.

Part 1 of the study was a double-blind, 52-week long extension with tadalafil 20 or 40 mg administered once daily to subjects with PAH. Part 2 is an open-label phase of tadalafil 40 mg once daily.



This interim report represents an interim database lock of 125 subjects who completed Part 1, all enrolled subjects who discontinued, and all enrolled subjects who were ongoing as of the October 4, 2007 cut-off date. The treatment period for Part 2 is ongoing.

Study population

Subjects were those who participated in the base study LVGY. Only subjects in the base study randomized to tadalafil 40 mg and experienced clinical worsening were not eligible.

After signing the informed consent form, subjects who met all eligibility criteria were assigned to receive tadalafil 20 or 40 mg once daily for 52 weeks based on their treatment assignment and response to therapy in Study LVGY as described below.

The following subjects were assigned to tadalafil 40 mg in Part 1:

- subjects who discontinued study LVGY because of clinical worsening and were taking placebo or tadalafil less than 40 mg;

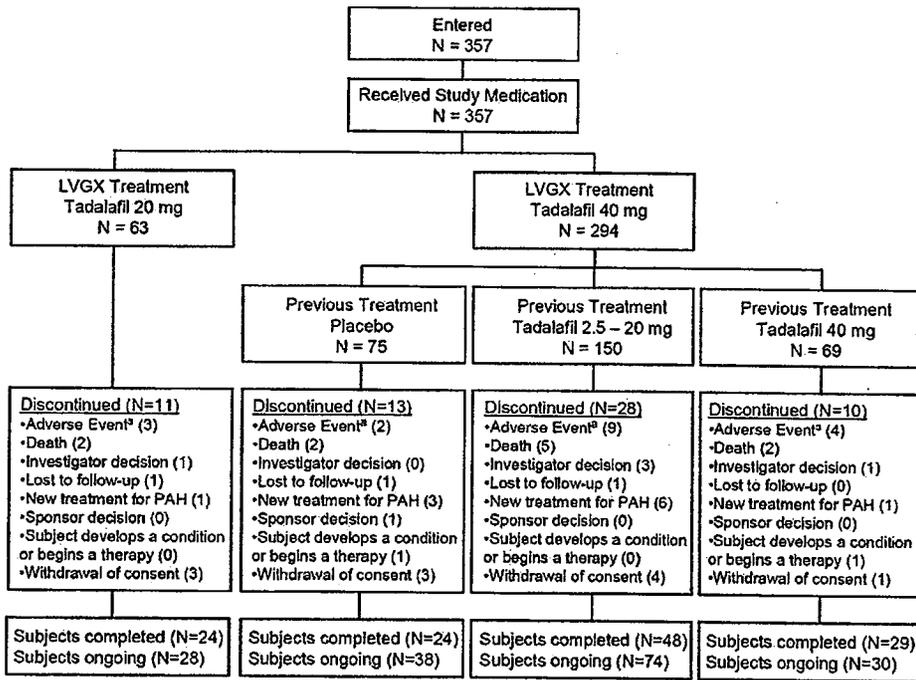
- subjects who had clinical worsening at Week 16 visit in study LVGY and were taking placebo or tadalafil less than 40 mg;
- subjects who completed Study LVGY without clinical worsening and were taking placebo or any dose of tadalafil.

The following subjects were to receive tadalafil 20 mg in Part 1:

- subjects who completed study LVGY without clinical worsening and were taking tadalafil 20 mg;
- investigator decided the subject did not tolerate the 40 mg dose of tadalafil.

Subject disposition

Of the 357 subjects who entered the extension study and received study drug, 63 (18%) received tadalafil 20 mg and 294 (82%) received tadalafil 40 mg.



Abbreviations: N = number of subjects; PAH = pulmonary arterial hypertension; WHO = World Health Organization.

* Adverse events (AEs) that led to discontinuation were hospitalization due to worsening of PAH, severe renal insufficiency, worsening of WHO functional class, and/or other AEs.

As of October 4, 2007, a total of 125 subjects completed part 1, 170 are ongoing and 62 were discontinued. Adverse events were the primary reason for discontinuation (18/357, 5%).

There were eleven reported deaths, eleven discontinuations because of adding new therapy for PAH, and eleven consents withdrawn.

Table LVGX.6.1. Study Disposition Summary by Randomized Study Treatment Group All Entered Subjects

		-----Tadalafil 40mg-----					TOTAL (N=357) n (%)
		T 20mg (N=63) n (%)	PiP1a (N=75) n (%)	Pi2.5-20mg (N=150) n (%)	P:40mg (N=69) n (%)	All T 40mg (N=294) n (%)	
Entered		63 (100)	75 (100)	150 (100)	69 (100)	294 (100)	357 (100)
Received Study Medication		63 (100)	75 (100)	150 (100)	69 (100)	294 (100)	357 (100)
Previous Placebo-control double-blind study	Clinical Worsening	0 (0.00)	8 (10.67)	11 (7.33)	0 (0.00)	19 (6.46)	19 (5.32)
	Completed 16-wk treatment Other	63 (100.00) 0 (0.00)	67 (89.33) 0 (0.00)	135 (90.00) 4 (2.67)	69 (100.00) 0 (0.00)	271 (92.18) 4 (1.36)	334 (93.56) 6 (1.12)
52-week Treatment Phase (Part 1)	Complete	24 (38.10)	24 (32.00)	48 (32.00)	29 (42.03)	101 (34.35)	125 (35.01)
	Early Discontinuation Ongoing	11 (17.46) 28 (44.44)	13 (17.33) 38 (50.67)	28 (18.67) 74 (49.33)	10 (14.49) 30 (43.48)	51 (17.35) 142 (48.30)	62 (17.37) 170 (47.62)
Reason Discontinued	Adverse Event	3 (4.76)	2 (2.67)	9 (6.00)	4 (5.80)	15 (5.10)	18 (5.04)
	- Hospitalization Due to Worsening of PAH	0 (0.00)	1 (1.33)	3 (2.00)	0 (0.00)	4 (1.36)	4 (1.12)
	- Other AE	3 (4.76)	1 (1.33)	4 (2.67)	3 (4.35)	8 (2.72)	11 (3.08)
	- Severe Renal Insufficiency	0 (0.00)	0 (0.00)	1 (0.67)	0 (0.00)	1 (0.34)	1 (0.28)
	- Worsening of WHO Functional Class	0 (0.00)	0 (0.00)	1 (0.67)	1 (1.45)	2 (0.68)	2 (0.56)
	Death	2 (3.17)	2 (2.67)	5 (3.33)	2 (2.90)	9 (3.06)	11 (3.08)
	Investigator Decision	1 (1.59)	0 (0.00)	3 (2.00)	1 (1.45)	4 (1.36)	5 (1.40)
Lost to Follow-up	1 (1.59)	1 (1.33)	1 (0.67)	0 (0.00)	2 (0.68)	3 (0.84)	

Abbreviations: N = number of entered subjects who have received study medication; n = number of subjects at the specified category. Prev = Actual received study treatment in the previous placebo-control double-blind study; P=Prev.

A total of 357 subjects entered into study LVGX and received study drug. There were 62 subjects who discontinued the study early, 125 who completed the 52-week phase, and 170 who are still participating in the trial. As of the cut off date, there were 11 reported deaths, 5 discontinued because of investigator decision, 3 were lost to follow up, 4 discontinued because of hospitalization for worsening PAH, 1 for severe renal insufficiency, and 2 for worsening WHO functional class.

There is little difference between the outcome for the 63 subjects who received tadalafil 20 mg and the 69 subjects who received tadalafil 40 mg for both the base study as well as the extension study.

There were 19 subjects who entered Study LVGX because of clinical worsening in the base study LVGY. Of these, 6 completed Part 1, 4 are continuing in Part 1, 3 died, 3 discontinued because of receiving new chronic PAH treatment, and 3 discontinued because of an adverse event.

Demographics

Overall, the subjects had a mean age of 54 years, with 9% being at least 75, the majority were female (78%) and white (82%). The majority (51%) of subjects had had PAH for less than 4 years and the etiology of PAH was idiopathic for 62%. More than half of the subjects (54%) were receiving concomitant bosentan and the mean walk distance was 379 m for all subjects. Most subjects were either WHO functional class II (50%) or III (41%). The mean Borg dyspnea score was 3.6. The baseline characteristics were similar for the treatment groups.

Efficacy

Although this was designed to be primarily a safety study, the 6 minute walk test was evaluated at baseline and weeks 16, 28, 40, and 52. The means for the walk distances are shown below by treatment group at baseline and week 52.

Mean walk distances (m)/sample size

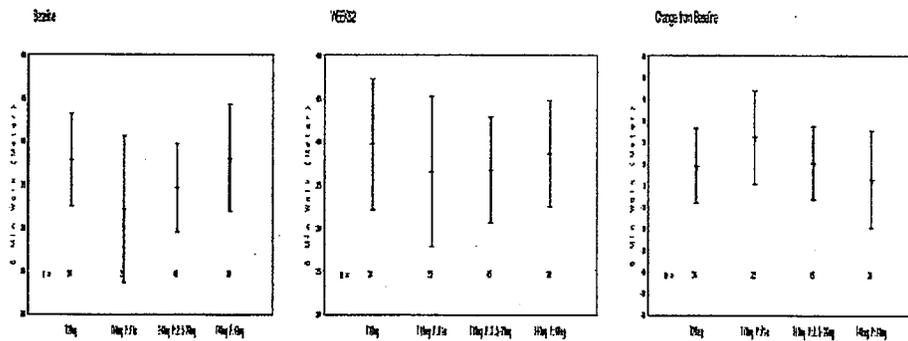
	Tadalafil 20 mg walk distance/sample size	Tadalafil 40 mg+ walk distance/sample size
Baseline	398/63	375/287
Week 52	399/24	384/100
Endpoint	405/58	381/273

+includes subjects who did not receive 40 mg in the base study.

LVGX.7.1

By the endpoint, these 2 groups were little changed from their baseline walk distances. The figure below shows the walk test at baseline, week 52 and change from baseline at week 52.

6-minute Walk Distance (meters) by Visit
Summary by Study Treatment and Study Treatment in Previous Study
All Subjects Entered and Received Study Treatment (N=357)
Study H6D-MC-LVGX (Interim 1)



Change from baseline was approximately 0 m for those subjects who were randomized to tadalafil 40 mg in the base study and remained on it for a total of 52 weeks (n=98).

Concomitant bosentan use

There were 53 subjects who were on bosentan during the base study and received tadalafil 40 mg for 52 weeks. The mean walk distance at 52 weeks for these subjects (n=54) was 387 m (mean walk distance at first visit of study LVGX was 379 m¹⁶).

There were 45 subjects who were not on bosentan during the base study and received tadalafil 40 mg for 52 weeks. The mean walk distance at 52 weeks for these subjects (n=44) was 380 m (mean walk distance at first visit of study LVGX was 367 m¹⁷).

¹⁶ Table 2.1 dated 9-29-08

WHO functional class

At the start of the extension study, 4% were class I, 50% were class II, 41% were class III, and 5% were class IV.

At week 52

The change in WHO functional class for subjects recorded at Week 52 was 12 (9%) reported worsening, 88 (69%) reported no change, and 27 (22%) reported improved. Of the 27 subjects who reported as improved, 2 improved by 2 classes and the rest improved by 1 class.

Subjects taking the tadalafil 20 mg dose throughout the base and extension studies reported 4 (17%) worsening, 17 (71%) no change and 3 (13%) improved. The subjects taking the tadalafil 40 mg dose throughout the base and extension studies reported 3 (10%) worsening, 21 (72%) no change, and 5 (17%) improved.

At endpoint

The table below shows the change from baseline at endpoint for the tadalafil 20 mg and the all 40 mg groups.

No. and (percent) of subjects

	Tadalafil 20 mg N=60	Tadalafil 40 mg+ N=66
Grew worse	10 (17)	6 (9)
No change	42 (70)	52 (79)
Improved	8 (13)	8 (12)

+ Received 40 mg dose through base and extensions studies

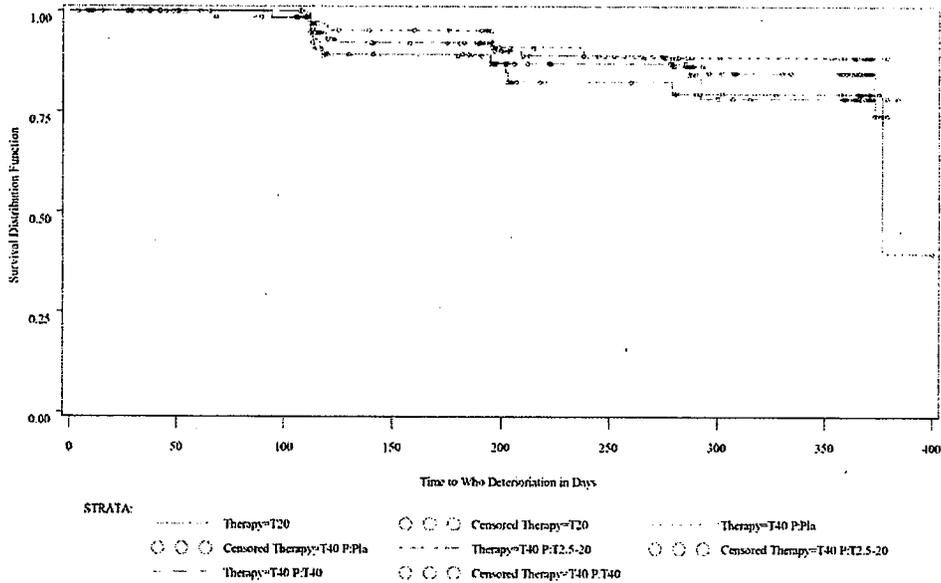
There were more subjects (10, 17%) who grew worse while taking tadalafil 20 mg compared to those taking 40 mg (6, 9%). The numbers who improved were similar for both groups.

Time to WHO functional class deterioration

The Kaplan-Meier plot for time to deterioration is shown below.

¹⁷ Table 2.2 dated 9-29-08

Kaplan-Meier Estimated Survival Curves of WHO Functional Class Deterioration
 Summary and Analysis by Study Treatment and Study Treatment in Previous Study
 All Subjects Entered and Received Study Treatment (N=357)
 Study H6D-MC-LVGX

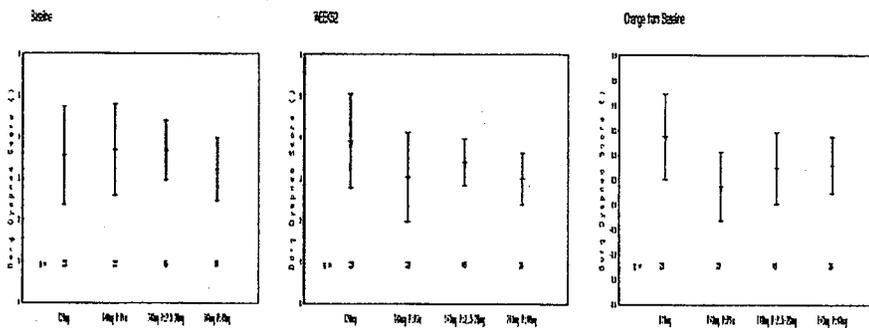


The times to WHO functional class deterioration were similar regardless of treatment.

Borg dyspnea score

Borg scores obtained at baseline, week 52, and change from baseline at endpoint are shown below for study subjects by treatment group.

Borg Dyspnea Score by Visit
 Summary by Study Treatment and Study Treatment in Previous Study
 All Subjects Entered and Received Study Treatment (N=357)
 Study H6D-MC-LVGX (Interim 1)



There is little difference between treatment groups at any of these time points.

Safety

Duration of exposure

There were 352 subjects who received at least one dose of study drug (62 tadalafil 20 mg and 290 tadalafil 40 mg). The mean number of days subjects spent on tadalafil 20 mg or 40 mg was approximately 250 days. There were 26 subjects who received tadalafil 40 mg for at least 360 days.

Serious safety

The subjects experiencing death, serious adverse events, discontinuation because of an adverse event and treatment emergent adverse events are shown in the table below.

**Table LVGX.8.3. Overview of Adverse Events
Study Treatment and Study Treatment in Previous Study
All Subjects Who Entered and Received Study Treatment**

Adverse Event ^a	T20 (N=63)		T40 P:Pla (N=75)		T40 P:T2.5-20 (N=150)		T40 P:T40 (N=69)		All T40 (N=294)		TOTAL (N=357)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Deaths ^b	2	(3.2)	2	(2.7)	5	(3.3)	2	(2.9)	9	(3.1)	11	(3.1)
Serious Adverse Events	13	(20.6)	20	(26.7)	40	(26.7)	10	(14.5)	70	(23.8)	83	(23.2)
Discontinuations due to an Adverse Event	5	(7.9)	4	(5.3)	14	(9.3)	6	(8.7)	24	(8.2)	29	(8.1)
Treatment Emergent Adverse Events	56	(88.9)	64	(85.3)	131	(87.3)	61	(88.4)	256	(87.1)	312	(87.4)

Abbreviations: N = number of entered subjects who have received study medication; n = number of subjects per category; TEAE = treatment-emergent adverse event; Prev = actual received study treatment in previous placebo-control double-blind study; P = Prev; T2.5-20 = Tadalafil 2.5-20mg; T20 = Tadalafil 20mg; T40 = Tadalafil 40mg.

^a - Subjects may be counted in more than one category.

^b - Deaths are also included as serious adverse events and discontinuations due to adverse events.

^c - Includes events that were considered possibly related to study drug as judged by the investigator.

There were 11 (3%) deaths reported during the extension study. There were 83 subjects who reported one or more serious adverse events and 29 subjects who discontinued study drug because of an adverse event (s). Nearly all patients (87%) reported at least one adverse event.

The tadalafil 20 mg (n=63) and the 40 mg (n=69) groups were similar in the reporting of deaths, discontinuations for adverse events and treatment emergent adverse events. The reporting of serious adverse events, however, was somewhat more frequent in the tadalafil 20 mg group (21% compared to 15%).

Deaths

The eleven subjects who were reported to have died during the extension study () are shown in the table below. All but 2 had been on tadalafil 40 mg at the time of death.

b(6)

Table LVGX.8.4. Deaths
Listing of All Subjects
All Subjects Who Entered and Received Study Treatment

Inv	Sub	Trt	Prev Trt	Cause of Death (Preferred Term)	Date of Death	Date of Randomization	Study day
114	1661	Tadalafil 40mg	Tadalafil 10mg	LUNG ADENOCARCINOMA			169
115	1701	Tadalafil 40mg	Tadalafil 10mg	PNEUMONIA			11
120	1954	Tadalafil 40mg	Placebo	CARDIAC ARREST	7	7	9
127	2301	Tadalafil 20mg	Tadalafil 20mg	DEATH			260
132	2556	Tadalafil 40mg	Tadalafil 2.5mg	MYOCARDIAL INFARCTION			140
201	4004	Tadalafil 40mg	Tadalafil 10mg	RIGHT VENTRICULAR FAILURE			8
503	5701	Tadalafil 40mg	Tadalafil 2.5mg	RIGHT VENTRICULAR FAILURE			210
505	5801	Tadalafil 40mg	Tadalafil 40mg	PNEUMONIA	2	W	38
601	6602	Tadalafil 20mg	Tadalafil 20mg	SUDDEN DEATH			141
601	6617	Tadalafil 40mg	Placebo	SUDDEN CARDIAC DEATH			160
601	6621	Tadalafil 40mg	Tadalafil 40mg	SUDDEN CARDIAC DEATH			4

b(6)

Abbreviations: N = number of entered subjects who have received study medication; Inv = Investigator; Sub = Subject; Trt = Actual received study treatment; Prev Trt = Actual received study treatment in previous placebo-control double-blind study.

Of the subjects who died, there were 4 reports of sudden deaths/cardiac arrest, 2 reports of right ventricular failures, 2 reports of pneumonia, 1 myocardial infarction, 1 reported as death¹⁸, and 1 lung carcinoma. All but 2 had been taking tadalafil during the base study.

Subject 601 6621 experienced sudden death after 4 days in the extension study. He had been on 40 mg during the base study.

Subject 120 1954 experienced cardiac arrest after 9 days in the extension study. This was a 52 year old female with scleroderma, Sjogren's disease, rheumatoid arthritis, Raynaud's syndrome, Hashimoto's thyroiditis and chronic inflammatory demyelinating paraneuropathy. She had been hospitalized for diarrhea and pedal edema during the base study. One week after receiving the first dose of tadalafil in the extension study, she was hospitalized for deterioration. The subject died from cardiac arrest nine days after starting tadalafil 40 mg. She had been randomized to placebo during the base study.

Subject 201 4004 experienced right ventricular failure after 8 days in the extension study. He had been on tadalafil 10 mg during the base study.

Subject 132 2556 was a 40 year old female with a history of multiple myeloma. She was discontinued from study drug after she developed renal failure. She died of multi-organ failure about one month later.

The remaining deaths were reported in subjects who had died of pneumonia (2) or had been on study drug at least 141 days.

Adverse events leading to study drug discontinuation

There were 29 subjects who discontinued study drug because of an adverse event. Adverse events that led to discontinuation in more than one subject included pulmonary hypertension (4), right ventricular failure (4), pneumonia (2), and sudden cardiac death (2).

Serious adverse events

¹⁸ Found dead at home, possible suicide, no other details available.

Serious adverse events reported by at least 2 tadalafil subjects are shown below.

Table LVGX.8.5. Serious Adverse Events by Preferred Term in Descending Order of Incidence Study Treatment and Study Treatment in Previous Study All Subjects Who Entered and Received Study Treatment

Preferred Term	T20 (N=63) n (%)	T40 P:Pla (N=75) n (%)	T40 P:T2.5-20 (N=150) n (%)	T40 P:T40 (N=69) n (%)	All T40 (N=294) n (%)	TOTAL (N=357) n (%)
Patients with >= 1 Serious AE	13 (20.6)	20 (26.7)	40 (26.7)	10 (14.5)	70 (23.8)	83 (23.2)
PULMONARY HYPERTENSION	1 (1.6)	2 (2.7)	4 (2.7)	2 (2.9)	8 (2.7)	9 (2.5)
RIGHT VENTRICULAR FAILURE	0 (0.0)	5 (6.7)	3 (2.0)	1 (1.4)	9 (3.1)	9 (2.5)
PNEUMONIA	0 (0.0)	0 (0.0)	4 (2.7)	2 (2.9)	6 (2.0)	6 (1.7)
CHEST PAIN	1 (1.6)	0 (0.0)	3 (2.0)	1 (1.4)	4 (1.4)	5 (1.4)
ANEMIA	1 (1.6)	1 (1.3)	1 (0.7)	0 (0.0)	2 (0.7)	3 (0.8)
NON-CARDIAC CHEST PAIN	1 (1.6)	1 (1.3)	1 (0.7)	0 (0.0)	2 (0.7)	3 (0.8)
EDEMA PERIPHERAL	0 (0.0)	1 (1.3)	2 (1.3)	0 (0.0)	3 (1.0)	3 (0.8)
ANGINA PECTORIS	1 (1.6)	0 (0.0)	0 (0.0)	1 (1.4)	1 (0.3)	2 (0.5)
ARTHRALGIA	1 (1.6)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.3)	2 (0.5)
CARDIAC FAILURE	0 (0.0)	2 (2.7)	0 (0.0)	0 (0.0)	2 (0.7)	2 (0.5)
DEHYDRATION	1 (1.6)	1 (1.3)	0 (0.0)	0 (0.0)	1 (0.3)	2 (0.5)
DIABETES MELLITUS	1 (1.6)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.3)	2 (0.5)
DIARRHOEA	1 (1.6)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.3)	2 (0.5)
DYSPHOEA	1 (1.6)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.3)	2 (0.5)
GASTROINTESTINAL HAEMORRHAGE	1 (1.6)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.3)	2 (0.5)
HAEMOPTYSIS	0 (0.0)	0 (0.0)	2 (1.3)	0 (0.0)	2 (0.7)	2 (0.5)
OSTEOARTHRITIS	1 (1.6)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.3)	2 (0.5)
PAIN IN EXTREMITY	1 (1.6)	1 (1.3)	0 (0.0)	0 (0.0)	1 (0.3)	2 (0.5)
PALPITATIONS	1 (1.6)	0 (0.0)	0 (0.0)	1 (1.4)	1 (0.3)	2 (0.5)
PERIPHERAL EDEMA	0 (0.0)	0 (0.0)	2 (1.3)	0 (0.0)	2 (0.7)	2 (0.5)
SUDDEN CARDIAC DEATH	0 (0.0)	1 (1.3)	0 (0.0)	1 (1.4)	2 (0.7)	2 (0.5)

Abbreviations: N = number of entered subjects who have received study medication; n = number of subjects with at least one serious adverse event; Prev = Actual received study treatment in previous placebo-control double-blind study; P = Prev; T2.5-20 = Tadalafil 2.5-20mg; T20 = Tadalafil 20mg; T40= Tadalafil 40mg.

Commonly reported serious adverse events included pulmonary hypertension (9), right ventricular failure (9), pneumonia (6), and chest pain (5). Events reported by 3 subjects included anemia, non-cardiac chest pain, and peripheral edema. These are serious events frequently reported by this type of subject population.

There was one report each of renal failure, acute renal failure, toxic hepatitis, and pancreatitis.

Renal failure

132 2556 This was a 40 year old white female whose past medical history included scleroderma, hypertension, reflux esophagitis, diarrhea, multiple myeloma, Raynaud's phenomenon, multiple myeloma, and depression. Concomitant medications included bosentan, warfarin, hydroxychloroquine, gabapentin, bupropion, lisinopril, rabeprazole, mupirocin, levofloxacin, and codeine/paracetamol. The subject was found to have renal insufficiency with a creatinine of 6.4 mg/dL and a BUN of 50 mg/dL. Upon review of past laboratory results, the investigator found her to have had increasing creatinine levels (1.3 mg/dL eight months previously). Dialysis was recommended. She was seen by the investigator one week later and was admitted for renal failure. Multiple renal cysts were found on ultrasound and biopsy findings were consistent with acute and chronic thrombotic microangiopathy, probably related to scleroderma renal disease. Study drug was discontinued. She died about one month later of myocardial infarction/multi-organ failure.

Acute renal failure

702-6901 This was an 87 year old female with a history of diabetes mellitus type I, chronic glaucoma, optic neuropathy, atrial fibrillation, pulmonary hypertension grade I, and acute tricuspid insufficiency grade II with moderate dilatation of the right atrium. Concomitant

medications included nifedipine, spironolactone, bosentan, acenocoumarol, glizalizer, and digoxin. The subject was hospitalized 133 days after beginning tadalafil because of acute lithiasis cholecystitis. Acute renal failure was reported ten days later. A cholecystectomy was performed successfully. Final diagnosis included acute lithiasis cholecystitis, normocytic anemia and chronic renal insufficiency.

Toxic hepatitis

601 6605 This was a 28 year-old female subject with concomitant medications including bosentan, nifedipine, furosemide, potassium canrenoate, digoxin, warfarin sodium. Approximately nine months after receiving the first dose of tadalafil, she experienced toxic hepatitis with nausea and subicterus. The patient was hospitalized with elevated hepatic enzymes. Bosentan was discontinued and the subject recovered.

Elevated liver enzymes and low creatinine clearance
129 2403. This was a 74 year old taking concomitant bosentan.

All adverse events

Adverse events reported by at least 3% of the total tadalafil subjects are shown below.

Table LVGX.8.8. Treatment-Emergent Adverse Events Occurring in Greater than or Equal to 3.0% of Subjects | Preferred Term in Descending Order of Incidence Comparison of Treatment Groups All Subjects Who Entered and Received Study Treatment

Preferred Term	T20 (N=63)		T40 P: P1a (N=75)		T40 P: T2.5-20 (N=150)		T40 P: T40 (N=69)		All T40 (N=294)		TOTAL (N=357)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients with ≥ 1 TEAE												
HEADACHE	9	(14.3)	21	(28.0)	37	(24.7)	10	(14.5)	68	(23.1)	77	(21.6)
DIARRHOEA	5	(7.9)	6	(8.0)	18	(12.0)	9	(13.0)	33	(11.2)	38	(10.6)
BACK PAIN	2	(3.2)	11	(14.7)	17	(11.3)	5	(7.2)	33	(11.2)	35	(9.8)
OEDEMA PERIPHERAL	5	(7.9)	7	(9.3)	17	(11.3)	6	(8.7)	30	(10.2)	35	(9.8)
UPPER RESPIRATORY TRACT INFECTION	7	(11.1)	5	(6.7)	13	(8.7)	9	(13.0)	27	(9.2)	34	(9.5)
DIZZINESS	2	(3.2)	8	(10.7)	20	(13.3)	3	(4.3)	31	(10.5)	33	(9.2)
PALPITATIONS	3	(4.8)	4	(5.3)	19	(12.7)	5	(7.2)	28	(9.5)	31	(8.7)
DYSPNOEA	5	(7.9)	5	(6.7)	13	(8.7)	7	(10.1)	25	(8.5)	30	(8.4)
PULMONARY HYPERTENSION	2	(3.2)	5	(6.7)	12	(8.0)	8	(11.6)	25	(8.5)	27	(7.6)
DYSPEPSIA	5	(7.9)	5	(6.7)	12	(8.0)	3	(4.3)	20	(6.8)	25	(7.0)
PAIN IN EXTREMITY	5	(7.9)	7	(9.3)	10	(6.7)	2	(2.9)	19	(6.5)	24	(6.7)
COUGH	3	(4.8)	7	(9.3)	7	(4.7)	6	(8.7)	20	(6.8)	23	(6.4)
NASOPHARYNGITIS	2	(3.2)	8	(10.7)	6	(4.0)	7	(10.1)	21	(7.1)	23	(6.4)
NAUSEA	3	(4.8)	4	(5.3)	10	(6.7)	6	(8.7)	20	(6.8)	23	(6.4)

Preferred Term	T20 (N=63)		T40 P: P1a (N=75)		T40 P: T2.5-20 (N=150)		T40 P: T40 (N=69)		All T40 (N=294)		TOTAL (N=357)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
FATIGUE	3	(4.8)	4	(5.3)	7	(4.7)	8	(11.6)	19	(6.5)	22	(6.2)
INSOMNIA	4	(6.3)	5	(6.7)	7	(4.7)	5	(7.2)	17	(5.8)	21	(5.9)
CHEST PAIN	3	(4.8)	3	(4.0)	8	(5.3)	6	(8.7)	17	(5.8)	20	(5.6)
EPISTAXIS	5	(7.9)	5	(6.7)	8	(5.3)	2	(2.9)	15	(5.1)	20	(5.6)
FLUSHING	3	(4.8)	8	(10.7)	5	(3.3)	4	(5.8)	17	(5.8)	20	(5.6)
ANASTHESIA	3	(4.8)	3	(4.0)	10	(6.7)	1	(1.4)	14	(4.8)	17	(4.8)
NASAL CONGESTION	1	(1.6)	5	(6.7)	5	(3.3)	6	(8.7)	16	(5.4)	17	(4.8)
VISION BLURRED	5	(7.9)	4	(5.3)	6	(4.0)	2	(2.9)	12	(4.1)	17	(4.8)
MYALGIA	4	(6.3)	5	(6.7)	4	(2.7)	3	(4.3)	12	(4.1)	16	(4.5)
RASH	4	(6.3)	5	(6.7)	3	(2.0)	4	(5.8)	12	(4.1)	16	(4.5)
MUSCLE SPASMS	3	(4.8)	2	(2.7)	8	(5.3)	2	(2.9)	12	(4.1)	15	(4.2)
ARTHRALGIA	1	(1.6)	2	(2.7)	10	(6.7)	1	(1.4)	13	(4.4)	14	(3.9)
DEPRESSION	2	(3.2)	4	(5.3)	3	(2.0)	4	(5.8)	11	(3.7)	13	(3.6)
HYPOKALAEMIA	1	(1.6)	3	(4.0)	3	(2.0)	4	(5.8)	11	(3.7)	12	(3.4)
SINUSITIS	1	(1.6)	2	(2.7)	6	(4.0)	3	(4.3)	11	(3.7)	12	(3.4)
URINARY TRACT INFECTION	1	(1.6)	6	(8.0)	3	(2.0)	2	(2.9)	11	(3.7)	12	(3.4)
WEIGHT INCREASED	3	(4.8)	1	(1.3)	4	(2.7)	4	(5.8)	9	(3.1)	12	(3.4)

Preferred Term	T20 (N=63)		T40 P: P1a (N=75)		T40 P: T2.5-20 (N=150)		T40 P: T40 (N=69)		All T40 (N=294)		TOTAL (N=357)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
ANXIETY	1	(1.6)	3	(4.0)	5	(3.3)	2	(2.9)	10	(3.4)	11	(3.1)
BRONCHITIS	2	(3.2)	1	(1.3)	4	(2.7)	4	(5.8)	9	(3.1)	11	(3.1)
OEDEMA	3	(4.8)	0	(0.0)	5	(3.3)	3	(4.3)	8	(2.7)	11	(3.1)

Abbreviations: N = number of entered subjects who have received study medication; n = number of subjects with at least 1 TEAE; TEAE = treatment-emergent adverse event; Prev = actual received study treatment in previous placebo-control double-blind study; P = Prev; T2.5-20 mg = Tadalafil 2.5-20 mg; T20 = Tadalafil 20 mg; T40 = Tadalafil 40 mg.
* Subjects may be counted in more than 1 category. Baseline is the run-in period (Visit 1-2) prior to randomization in the previous placebo-controlled double-blind study.

The most commonly reported events included headache (22%), diarrhea (11%), back pain (10%), peripheral edema (10%), URI (10%). Many of the events are included in the adverse events reported for the erectile dysfunction indication (headache, dyspepsia, back pain, myalgia, nasal congestion, flushing, and pain in limb).

Subpopulations

Gender

The most commonly reported adverse events by females across all tadalafil treatment groups were headache, diarrhea, back pain, dizziness, upper respiratory tract infection, palpitations, peripheral edema, pulmonary hypertension, and nausea. The most commonly reported adverse events reported by males across all tadalafil treatment groups were dyspnea, headache, nasopharyngitis, peripheral edema, diarrhea, dyspepsia, and pain in extremity.

Age

The most commonly reported adverse events by subjects <65 years of age were headache, upper respiratory tract infection, dizziness, peripheral edema, palpitations, diarrhea, back pain, dyspnea, pulmonary hypertension, and dyspepsia. The most commonly reported adverse events by subjects ≥65 years of age were headache, diarrhea, back pain, peripheral edema, dyspnea, and pain in extremity. The most commonly reported adverse events in subjects ≥75 years of age were headache, back pain, diarrhea, dizziness, macular degeneration, bronchitis, nausea, peripheral edema, and right ventricular failure.

Bosentan Use

The most commonly reported adverse events by those not taking bosentan are shown below followed by the most commonly reported adverse events by those taking bosentan.

Summary of Treatment Emergent Adverse Events by Preferred Term in Descending Order of Incidence in the Total Tadalafil Summary by Study Treatment and Study Treatment in Previous Study
All Subjects Entered and Received Study Treatment with No Bosentan Use (N=165)
Study H6D-NC-LV0X (Interim 1)

Preferred Term	T20	T40 P:P1a	T40 P:T2.5-20	T40 P:T40	All T40	TOTAL
	(N=26) n (%)	(N=34) n (%)	(N=73) n (%)	(N=32) n (%)	(N=139) n (%)	(N=165) n (%)
Patients with >= 1 TEAE	25 (96.2)	26 (76.5)	64 (87.7)	27 (84.4)	117 (84.2)	142 (86.1)
HEADACHE	6 (23.1)	7 (20.6)	16 (21.9)	3 (9.4)	26 (19.7)	32 (19.4)
DIARRHOEA	3 (11.5)	2 (5.9)	11 (15.1)	5 (15.6)	18 (12.9)	21 (12.7)
OEDEMA PERIPHERAL	4 (15.4)	3 (8.8)	11 (15.1)	2 (6.3)	16 (11.5)	20 (12.1)
DIZZINESS	1 (3.8)	6 (17.6)	10 (13.7)	2 (6.3)	18 (12.9)	19 (11.5)
DYSPNOEA	2 (7.7)	2 (5.9)	7 (9.6)	6 (18.8)	15 (10.8)	17 (10.3)
UPPER RESPIRATORY TRACT INFECTION	3 (11.5)	4 (11.8)	5 (6.8)	5 (15.6)	14 (10.1)	17 (10.3)
PALPITATIONS	1 (3.8)	4 (11.8)	8 (11.0)	3 (9.4)	15 (10.8)	16 (9.7)

Summary of Treatment Emergent Adverse Events by Preferred Term in Descending Order of Incidence in the Total Tadalafil Summary by Study Treatment and Study Treatment in Previous Study
 All Subjects Entered and Received Study Treatment with Bosentan Use (N=192)
 Study H6D-NC-LVGY (Interim 1)

Preferred Term	T20	T40 P:Pla	T40 P:T2.5-20	T40 P:T40	All T40	TOTAL
	(N=37)	(N=41)	(N=77)	(N=37)	(N=155)	(N=192)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients with >= 1 TEAE	31 (83.8)	38 (92.7)	67 (87.0)	34 (91.9)	139 (89.7)	170 (88.5)
HEADACHE	3 (8.1)	14 (34.1)	21 (27.3)	7 (18.9)	42 (27.1)	45 (23.4)
BACK PAIN	1 (2.7)	8 (19.5)	9 (11.7)	4 (10.8)	21 (13.5)	22 (11.5)
DYSPEPSIA	5 (13.5)	3 (7.3)	9 (11.7)	2 (5.4)	14 (9.0)	19 (9.9)
DIARRHOEA	2 (5.4)	4 (9.8)	7 (9.1)	4 (10.8)	15 (9.7)	17 (8.9)
PAIN IN EXTREMITY	3 (8.1)	5 (12.2)	8 (10.4)	1 (2.7)	14 (9.0)	17 (8.9)
UPPER RESPIRATORY TRACT INFECTION	4 (10.8)	1 (2.4)	8 (10.4)	4 (10.8)	13 (8.4)	17 (8.9)

The reported events were similar for the two groups as were the incidence rates.

Bleeding events

A total of 53 subjects reported bleeding events including epistaxis (20, 6%), contusion (6, 2%), hematoma (4, 1%), and menorrhagia (4, 1%). There were 3 subjects who reported retinal or eye hemorrhage.

Clinical laboratory values

Hematology

There were 3 serious adverse event reports of anemia, none that led to study drug discontinuation.

Renal function

There was one discontinuation for increased creatinine (503-5706).

Liver function

There was one discontinuation for abnormal liver function tests (129 2403, subject was taking bosentan).

Two subjects (303-4302 and 601-6605) reported >5 times (and >3 times) ULN for both serum AST and ALT; both subjects received bosentan.

Subject 601-6601 had >3 times ULN for serum AST and >5 times (and >3 times) ULN for serum ALT.

Subject 601-6616 had >3 times ULN for both serum AST and ALT.

Subject 118-1854 had >5 times (and >3 times) ULN for serum AST; subject discontinued prematurely because of peripheral edema.

Subject 129-2403 had >3 times ULN for serum AST and >1.5 times ULN for serum bilirubin and was discontinued prematurely (bosentan was concomitant medication):

Subject 105-1201 had >3 times ULN for serum AST; subject discontinued prematurely because of sinusitis.

These subjects were not taking bosentan:

Subject 105-1201 had a history of hepatitis C virus infection, esophageal varices, and repair of esophageal varices. At baseline of Study LVGY, the subject had an elevated serum AST and ALT.

Subject 118-1854 had a history of hyperbilirubinemia, fatty liver, elevated serum enzymes, and alcohol abuse. At baseline of Study LVGY, the subject had an elevated serum AST and an elevated serum bilirubin.

Subject 601-6601 was a 69-year-old female with normal serum AST and bilirubin levels at baseline; ALT levels were slightly elevated. There was a transient increase in aminotransferases without an increase of bilirubin. Liver chemistry assessments were normal during the next two visits but slightly increased on Visit 8. The subject's bilirubin remained within normal limits at all times.

Subject 601-6616 had a history of hepatitis C virus infection and Gaucher's disease. At baseline of Study LVGY, the subject had an elevated serum AST/ALT and bilirubin.

Appendix 1

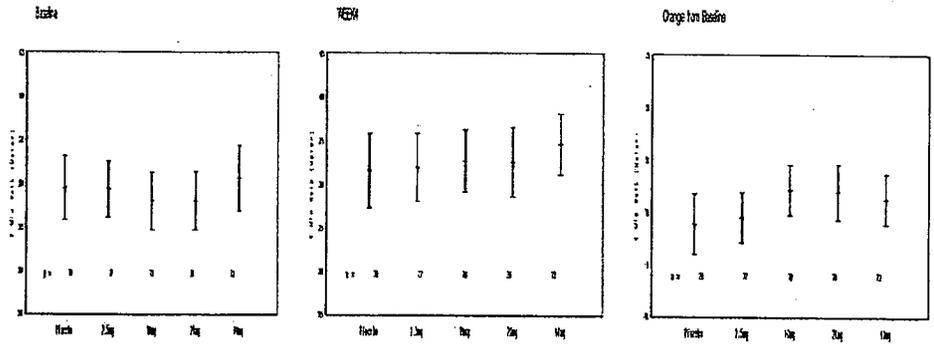
	tadalafil				
	Placebo n=79	2.5 mg n=79	10 mg n=78	20 mg n=80	40 mg n=76
Mean baseline walk distance (SD)	347.49 (81.18)	346.53 (71.60)	340.01(72.80)	338.26(74.45)	352.67(78.75)
Week 4					
# of subjects evaluated at week 4	79	77	78	78	72
Mean change from baseline at week 4 (SD)	10.47 (51.44)	12.91 (42.07)	23.54 (42.62)	22.87 (47.75)	20.03 (41.36)
Treatment effect	-	2.44	13.07	12.4	9.56
Week 8					
# of subjects evaluated at week 8	79	79	78	80	76
Mean change from baseline at week 8 (SD)	13.04 (48.79)	14.15 (46.02)	31.58 (50.63)	29.85 (52.21)	28.91 (45.74)
Treatment effect	-	1.11	18.54	16.81	15.87
Week 12					
# of subjects evaluated at week 12	79	79	78	80	76
Mean change from baseline at week 12 (SD)	10.14 (55.49)	14.42 (49.17)	34.20 (51.61)	35.60 (50.16)	36.25 (53.00)
Treatment effect	-	4.28	24.06	25.46	26.11
Week 16					
# of subjects evaluated at week 16	79	79	78	80	76

Mean change from baseline at week 16 (SD)	9.21 (59.96)	21.79 (60.83)	28.6 (62.17)	36.23 (47.53)	41.14 (49.39)
Treatment effect	-	12.58	19.39	27.02	31.93

LVGY 14.8

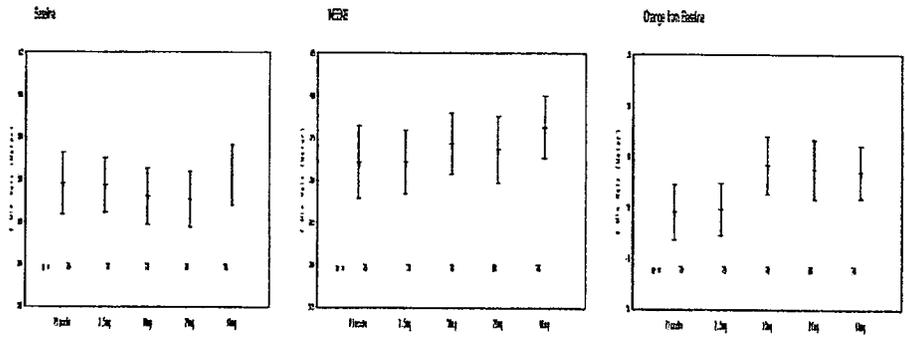
Week Four

6-minute Walk Distance (meters) by Visit, Last Non-missing Observation in Treatment Period Carried Forward
 Summary and Analysis by Randomized Study Treatment Group
 All ITT Subjects (N=405)
 Study H6D-MC-LVGY



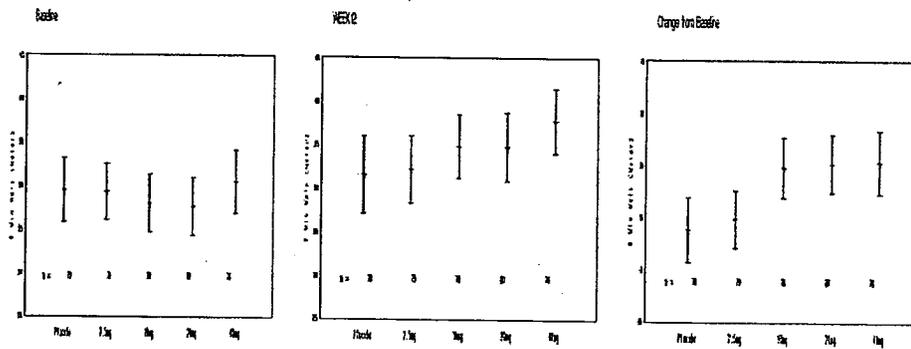
week 8

6-minute Walk Distance (meters) by Visit, Last Non-missing Observation in Treatment Period Carried Forward
 Summary and Analysis by Randomized Study Treatment Group
 All ITT Subjects (N=405)
 Study H6D-MC-LVGY



week 12

6-minute Walk Distance (meters) by Visit, Last Non-missing Observation
in Treatment Period Carried Forward
Summary and Analysis by Randomized Study Treatment Group
All ITT Subjects (N=405)
Study H6D-MC-LVGY



Appendix 2

Bosentan use

A total of 216 subjects (53%) were taking concomitant bosentan. The number of subjects taking bosentan was evenly distributed across treatment groups (41-45 per group).

6 min walk: Change from baseline at week 16 (m)

placebo		Tad 2.5mg		Tad 10mg		Tad 20mg		Tad 40mg	
yes+	no [^]	yes+	no [^]	yes+	no [^]	yes+	no [^]	yes+	no [^]
n=44	n=35	n=41	N=38	n=39	n=39	n=43	n=37	n=39	n=37
18.8	-2.9	22.7	20.8	26.6	30.6	41.5	30.1	40.2	42.2
<i>Trx effect</i>		3.9	23.7	7.8	33.5	22.7	33.0	21.4	45.1

Age

The table below shows the outcome of the 6 minute walk test for those subjects < 54 years old compared to those > 54 years old.

6 min walk: Change from baseline at week 16 (m)

placebo		Tad 2.5mg		Tad 10mg		Tad 20mg		Tad 40mg	
<54yrs	>54yrs	<54yrs	>54yrs	<54yrs	>54yrs	<54yrs	>54yrs	<54yrs	>54yrs
n=40	n=39	n=34	n=45	n=40	n=38	n=42	n=38	n=41	n=35
17	1	31	15	40	17	38	34	50	31
<i>Trx effect</i>		14	14	23	16	21	33	33	30

LVGY.11.11

Walking distances, minus the placebo effect, were similar for both age groups, regardless of dose.

Gender

6 min walk: Change from baseline at week 16 (m)

placebo		Tad 2.5mg		Tad 10mg		Tad 20mg		Tad 40mg	
F	M	F	M	F	M	F	M	F	M
n=62	n=17	n=61	n=18	n=65	n=13	n=60	n=20	n=57	n=19
8	14	14	50	26	43	35	40	42	40
<i>Trx effect</i>		6	36	18	29	27	26	34	26

LVGY.11.11

There were 3.5 times as many females as males. The treatment effect was similar for the females and males except for tadalafil 2.5 mg.

Baseline walk test

The subjects were grouped according to baseline 6 min walk distance (>325 m versus ≤325 m). Approximately twice the number of subjects walked more than 325 m at baseline compared to those who walked less than or equal to 325 m.

6 min walk:change from baseline at week 16(m)

placebo		Tad 2.5mg		Tad 10mg		Tad 20mg		Tad 40mg	
>325 n=51	≤325 n=28	>325 n=51	≤325 n=28	>325 n=51	≤325 n=27	>325 n=51	≤325 n=29	>325 n=51	≤325 n=25
8	12	23	19	22	41	36	37	33	57
Trx effect		15	7	14	29	28	25	25	45

Appendix 3

Table LVGY.11.8. Cardiopulmonary Hemodynamics Change from Baseline to End of Treatment ITT Subjects

Right Heart Catheterization		Placebo (N=16)	Tadalafil			
			2.5mg (N=24)	10mg (N=18)	20mg (N=17)	40mg (N=18)
Heart Rate (beats/min)	n	14	21	15	15	15
	Mean Change from baseline to Wk 16	-2.14	-1.19	-3.67	-4.93	2.60
	Week 16	69.36	74.10	73.27	73.20	73.20
	Baseline	71.50	75.29	76.93	79.13	70.60
	95% C.I.	-10.25, 5.96	-5.03, 2.63	-7.31, 0.0490	-8.21, -0.02	-2.42, 7.62
	p-value*	0.5776	0.5226	0.0490	0.0186	0.2856
Mean Pulmonary Artery Pressure (mmHg)	n	14	21	15	15	15
	Mean Change from baseline to Wk 16	-2.21	-3.29	-3.67	-8.47	-4.27
	Week 16	47.00	50.81	47.27	49.73	50.07
	Baseline	49.21	54.10	50.93	58.20	54.33
	95% C.I.	-7.24, 2.82	-6.25, -0.32	-7.60, 0.27	-12.55, -4.39	-7.53, -1.01
	p-value*	0.3589	0.0316	0.0655	0.0005	0.0140
Pulmonary Vascular Resistance (dyn*cm**5)	n	12	18	12	13	14
	Mean Change from baseline to Wk 16	11.00	-65.30	-140.3	-254.2	-209.2
	Week 16	838.17	785.21	702.21	317.69	691.49
	Baseline	927.17	951.52	942.56	971.85	900.70
	95% C.I.	-159.68, 181.69	-178.66, 48.06	-327.68, 46.98	-388.24, -120.1	-405.55, -12.88
	p-value*	0.8897	0.2408	0.1274	0.0014	0.0385

Abbreviations: N = number of randomized subjects who participated in the RRC sub study; n = number of subject with nonmissing data at baseline and Week 16; C.I. = confidence interval.

* paired t-test compare to baseline.

Right Heart Catheterization
Summary and Analysis by Randomized Study Treatment Group
All ITT Subjects (N=93)
Study H6D-MC-LVGY

Right Heart Catheterization		Placebo (N=16)	Tadalafil			
			2.5mg (N=24)	10mg (N=18)	20mg (N=17)	40mg (N=18)
Mean Right Atrial Pressure (mmHg)	n	14	21	15	15	15
	Mean Change from baseline to Wk 16	-0.79	-0.24	-0.60	-0.87	-1.20
	Week 16	6.50	7.14	6.13	5.80	6.93
	Baseline	7.29	7.38	6.73	6.67	8.13
	95% C.I.	-2.90, 1.33	-2.38, 1.90	-2.64, 1.44	-2.88, 1.15	-3.41, 1.01
	p-value*	0.4365	0.8188	0.5379	0.3724	0.2631
Cardiac Index (L/min/m**2)	n	12	19	12	13	14
	Mean Change from baseline to Wk 16	-0.01	0.14	0.21	0.20	0.36
	Week 16	2.43	2.59	2.83	2.76	2.93
	Baseline	2.44	2.45	2.62	2.56	2.57
	95% C.I.	-0.44, 0.41	-0.13, 0.41	-0.18, 0.59	-0.04, 0.44	0.09, 0.63
	p-value*	0.9436	0.2828	0.2668	0.0925	0.0126
Cardiac Output (L/min)	n	12	19	12	13	14
	Mean Change from baseline to Wk 16	-0.04	0.28	0.33	0.32	0.61
	Week 16	4.15	4.65	4.56	4.63	5.29
	Baseline	4.19	4.38	4.22	4.30	4.67
	95% C.I.	-0.77, 0.70	-0.24, 0.79	-0.28, 0.94	-0.09, 0.74	0.08, 1.14
	p-value*	0.9103	0.2714	0.2549	0.1173	0.0282

Abbreviations: N = number of randomized subjects who participated in the RRC sub study; n = number of subject with nonmissing data at baseline and Week 16; C.I. = confidence interval.

* paired t-test compare to baseline.

Right Heart Catheterization
 Summary and Analysis by Randomized Study Treatment Group
 All ITT Subjects (N=93)
 Study HED-MC-LVQY

Right Heart Catheterization		Placebo (N=16)	Tadalafil			
			2.5mg (N=24)	10mg (N=18)	20mg (N=17)	40mg (N=18)
Pulmonary Capillary Wedge Pressure (mmHg)	n	14	20	15	15	15
	Mean Change from Baseline to WK 16	-0.93	-1.40	0.67	-0.47	-0.07
	Week 16 Baseline	8.57	9.30	10.73	8.66	8.87
	95% C.I.	-3.06, 1.20	-5.20, 2.40	-3.11, 4.44	-2.72, 1.79	-2.04, 1.90
	p-value*	0.3635	0.4498	0.7107	0.6637	0.9431
Mean Arterial Pressure (mmHg)	n	14	21	15	15	15
	Mean Change from Baseline to WK 16	-5.00	-0.95	-1.93	-1.93	-2.00
	Week 16 Baseline	81.36	90.86	83.93	89.73	88.53
	95% C.I.	-13.74, 3.74	-6.00, 4.09	-8.85, 4.98	-10.44, 6.58	-9.54, 5.64
	p-value*	0.2382	0.6980	0.5581	0.6337	0.5832
Systemic Arterial O2 Saturation (%)	n	13	20	13	13	14
	Mean Change from Baseline to WK 16	0.23	0.30	0.23	1.69	0.14
	Week 16 Baseline	91.77	93.45	90.00	95.69	92.86
	95% C.I.	-1.55, 2.01	-1.06, 1.66	-2.64, 3.10	0.47, 2.91	-1.56, 1.85
	p-value*	0.7826	0.6493	0.8539	0.0105	0.8594

Abbreviations: N = number of randomized subjects who participated in the RHC sub study; n = number of subject with nonmissing data at baseline and Week 16; C.I. = confidence interval.

* paired t-test compare to baseline.

Right Heart Catheterization
 Summary and Analysis by Randomized Study Treatment Group
 All ITT Subjects (N=93)
 Study HED-MC-LVQY

Right Heart Catheterization		Placebo (N=16)	Tadalafil			
			2.5mg (N=24)	10mg (N=18)	20mg (N=17)	40mg (N=18)
Mixed Venous O2 Saturation (%)	n	13	20	13	12	13
	Mean Change from Baseline to WK 16	-0.15	2.10	0.77	6.75	3.15
	Week 16 Baseline	62.00	63.95	66.62	72.75	67.15
	95% C.I.	-4.34, 3.83	-0.28, 4.48	-2.75, 4.29	2.60, 10.90	-0.32, 6.63
	p-value*	0.9343	0.0800	0.6422	0.0043	0.0717
Systemic Vascular Resistance (dyn* ² /cm ⁵)	n	12	19	12	13	14
	Mean Change from Baseline to WK 16	-10.31	-118.5	-84.44	-159.4	-235.8
	Week 16 Baseline	1610.4	1602.8	1531.2	1538.7	1353.7
	95% C.I.	-268.55, 247.92	-302.00, 65.09	-349.79, 193.90	-430.98, 112.10	-546.13, 74.48
	p-value*	0.9315	0.1919	0.5381	0.2250	0.1246

Abbreviations: N = number of randomized subjects who participated in the RHC sub study; n = number of subject with nonmissing data at baseline and Week 16; C.I. = confidence interval.

* paired t-test compare to baseline.

Appendix 4

Table LVGY.11.9. SF-36v2 Health Survey
Change from Baseline to End of Treatment
ITT Subjects

SF-36v2 Health Survey		Placebo (N=82)	2.5mg (N=82)	10mg (N=80)	Tadalafil	
					20mg (N=82)	40mg (N=79)
Physical Functioning	n	76	74	74	76	77
	Mean Change from baseline to WK 16	-1.00	6.50	7.11	6.92	6.84
	Week 16 Baseline	37.43 38.44	44.90 38.39	42.77 35.66	45.41 38.48	46.11 41.27
	95% C.I. ^a	-5.15, 3.15	1.35, 11.66	3.03, 11.19	3.07, 10.77	2.73, 10.95
	p-value ^b		0.0084	0.0113	0.0052	0.0022
Role-Physical	n	77	73	74	75	76
	Mean Change from baseline to WK 16	2.92	7.71	8.59	7.58	12.80
	Week 16 Baseline	43.75 40.83	49.57 41.87	50.82 42.23	50.08 42.50	56.25 43.45
	95% C.I. ^a	-1.88, 7.72	1.78, 13.63	3.49, 13.69	1.83, 13.34	7.14, 18.46
	p-value ^b		0.1409	0.0773	0.1309	0.0021
Bodily Pain	n	76	74	75	73	77
	Mean Change from baseline to WK 16	1.13	0.35	1.52	1.99	10.27
	Week 16 Baseline	50.13 59.00	51.20 60.85	57.91 66.39	62.36 60.37	70.61 60.34
	95% C.I. ^a					
	p-value ^b					

Abbreviations: N = number of randomized subjects who participated in the RHC sub study; n = number of subject with nonmissing data at baseline and Week 16; Week 16 = Week 16 or Early Discontinuation; C.I. = confidence interval.

^a 95% C.I. is calculated paired t-test compare to baseline.

^b ANCOVA was used. The model included treatment group, PAH etiology, bosentan use, baseline 6-minute walk distance, and baseline value of each domain.

SF-36v2 Health Survey
Summary and Analysis by Randomized Study Treatment Group
All ITT Subjects (N=405)
study H6D-NC-LVGY

SF-36v2 Health Survey		Placebo (N=82)	2.5mg (N=82)	10mg (N=80)	Tadalafil	
					20mg (N=82)	40mg (N=79)
Bodily Pain	95% C.I. ^a	-4.08, 6.34	-6.49, 7.19	-3.58, 0.3149	-3.72, 6.62	4.98, 15.57
	p-value ^b			0.6991	0.0072	
General Health	n	76	73	75	75	77
	Mean Change from baseline to WK 16	-2.11	4.76	4.26	4.19	8.27
	Week 16 Baseline	44.46 46.57	44.47 39.71	44.93 40.67	43.84 39.65	46.43 38.16
	95% C.I. ^a	-6.07, 1.86	1.17, 8.35	0.53, 0.0503	0.82, 7.59	4.48, 12.06
	p-value ^b		0.0414	0.0671	0.0011	
Vitality	n	76	73	75	75	77
	Mean Change from baseline to WK 16	-0.82	7.73	5.72	8.53	6.90
	Week 16 Baseline	43.42 46.24	49.17 42.44	50.47 44.75	51.92 43.39	51.70 44.91
	95% C.I. ^a	-4.90, 3.25	3.35, 12.12	1.83, 0.0154	9.61, 0.0012	12.48, 2.31, 11.49
	p-value ^b		0.0067		0.0048	
Social Functioning	n	76	73	73	71	77

Abbreviations: N = number of randomized subjects who participated in the RHC sub study; n = number of subject with nonmissing data at baseline and Week 16; Week 16 = Week 16 or Early Discontinuation; C.I. = confidence interval.

^a 95% C.I. is calculated paired t-test compare to baseline.

^b ANCOVA was used. The model included treatment group, PAH etiology, bosentan use, baseline 6-minute walk distance, and baseline value of each domain.

SF-36v2 Health Survey
Summary and Analysis by Randomized Study Treatment Group
All ITT Subjects (N=405)
study H6D-NC-LVGY

SF-36v2 Health Survey		Placebo (N=82)	2.5mg (N=82)	10mg (N=80)	Tadalafil	
					20mg (N=82)	40mg (N=79)
Mental Health	p-value ^b		0.2064	0.3369	0.0262	0.0670
Mental Health	n	76	74	75	75	77
	Mean Change from baseline to WK 16	0.39	4.78	1.88	5.87	5.15
	Week 16 Baseline	64.58 64.69	64.58 62.27	66.10 64.27	73.39 70.89	67.78 63.38
	95% C.I. ^a	-6.17, 5.95	-4.27, 8.89	-5.21, 0.6800	-3.81, 0.86	-2.47, 11.24
	p-value ^b		0.7961		0.1866	0.3647
Mental Health	n	76	74	75	75	77
	Mean Change from baseline to WK 16	0.39	4.78	1.88	5.87	5.15
	Week 16 Baseline	67.04 66.64	68.09 61.31	71.93 70.05	73.20 67.33	70.84 65.70
	95% C.I. ^a	-2.85, 3.64	0.10, 9.46	-1.38, 5.15	2.35, 9.38	0.87, 9.42
	p-value ^b					

Abbreviations: N = number of randomized subjects who participated in the RHC sub study; n = number of subject with nonmissing data at baseline and Week 16; Week 16 = Week 16 or Early Discontinuation; C.I. = confidence interval.

^a 95% C.I. is calculated paired t-test compare to baseline.

^b ANCOVA was used. The model included treatment group, PAH etiology, bosentan use, baseline 6-minute walk distance, and baseline value of each domain.

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James Hung
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