2. LVGX Synopsis

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Clinical Study Report Synopsis: Study H6D-MC-LVGX

Title of Study: An Extension Study to Evaluate the Long-Term Safety and Efficacy of the Phosphodiesterase Type 5 (PDE5) Inhibitor Tadalafil in the Treatment of Patients with Pulmonary Arterial Hypertension

Number of Investigators: This multicenter study included 73 principal investigators.

Study Centers: This study was conducted at 73 study centers in 9 countries.

Publication(s) Based on the Study: None at this time.

Length of Study:
Date of first patient enrolled: 14 December 2006
Date of last patient completed: 27 February 2012

Phase of Development: 3

Objectives: The primary objective of the open-label extension (OLE) Part 2 of Study LVGX was to evaluate long-term safety of tadalafil while providing continued access to tadalafil for patients with PAH who completed Part 1 of the study.

Study Design: Part 2 of Study LVGX was a Phase 3, multicenter, open-label extension study to evaluate the long-term safety of tadalafil 40 mg in patients with pulmonary arterial hypertension (PAH). Patients entered Part 2 of Study LVGX after completing double-blind Part 1 of Study LVGX.

Number of Patients: A total of 286 patients with PAH entered open-label extension (OLE) LVGX Part 2; of these, 217 patients completed Part 2 and 69 patients discontinued prior to completion.

Diagnosis and Main Criteria for Inclusion: Patients with PAH were eligible for LVGX Part 2 if they completed Part 1.

Study Drug, Dose, and Mode of Administration:
All patients in LVGX Part 2 received open-label tadalafil 40 mg once a day. Tadalafil tablets were provided in bottles (Japan used blister packs). Patients were instructed to take 2 tablets orally each morning.

Item	Study Drug
Code number or chemical nomenclature	IC351, LY450190
Generic name or brand name	Tadalafil
Active ingredient and content	20 mg tablet contains 20 mg tadalafil
Formulation and appearance	Yellow, almond-shaped tablet debossed with “A6W8”
Treatment	40 mg (two 20-mg tablets)

Duration of Treatment:
Open-label treatment for LVGX Part 2 was provided until tadalafil became commercially available for the treatment of PAH, or if the Sponsor concluded the study. The study was concluded when marketed drug was available for participating patients.

Variables:
Efficacy: This study was not designed to assess efficacy and no efficacy analyses were preplanned in the study protocol or Statistical Analysis Plan. After the study was completed, however, events of PAH deterioration during Part 2 were defined retrospectively, and analyses of the PAH deterioration event rate were designed.
Safety: Deaths, serious adverse events (SAEs), adverse events (AEs) leading to discontinuation, and AEs. Vital signs data, electrocardiogram measurements, and laboratory data were not collected during LVGX Part 2.

Statistical Analyses:

Efficacy: Events of PAH deterioration were defined retrospectively from the LVGX Part 2 data as:

- Death
- Lung transplantation
- Atrial septostomy
- Starting a new, chronic treatment for PAH based on concomitant medication data
- Discontinuation from the study due to receiving a new treatment for PAH
- Discontinuation from the study due to hospitalization due to worsening PAH
- Discontinuation from the study due to worsening WHO functional class.

The incidence of PAH deterioration during LVGX Part 2 was summarized. Time-to-event analyses using Kaplan-Meier survival methods were tabulated for PAH deterioration.

Safety: Treatment exposure during LVGX Part 2 was estimated as the duration between the date of the first visit in LVGX Part 2 and the discontinuation date from LVGX Part 2.

A treatment-emergent adverse event was defined as an AE that first occurred or worsened in intensity after baseline, which was defined as the period prior to randomization and drug administration in Study LVGY.

The patient incidence of TEAEs was tabulated by preferred term, system organ class (SOC) and preferred term, and by maximum severity within SOC and preferred term. Additional summaries of TEAEs were tabulated by age group (<65 years of age and ≥65 years of age) and by gender. Procedure-related AEs, SAEs, and AEs leading to discontinuation were also tabulated. An additional summary of treatment-emergent bleeding events was provided. Time-to-event analyses using Kaplan-Meier survival methods were tabulated for all cause mortality. Listings of SAEs, AEs leading to discontinuation, and deaths were also provided.

Summary:

A total of 286 entered the Part 2 of this study from double-blind Part 1; of these, 217 patients completed Part 2 and 69 patients discontinued prior to completion. The most common reasons for discontinuation were death (40 patients, 14%), AEs (11 patients, 4%), withdrawal of consent (6 patients, 2%), and investigator decision (5 patients, 2%).

Total exposure to tadalafil during LVGX Part 2 was 638.5 patient-years. Most patients (97%) were exposed to study medication in LVGX Part 2 for at least 3 months; 12 patients (4%) were exposed to study drug for ≥48 months.

During LVGX Part 2, 93 patients (33%) experienced PAH deterioration. The most common reason for deterioration was initiation of new PAH therapy (66 patients, 23%) and death (40 patients, 14%). The probability of remaining event free (no PAH deterioration) ranged from 89% (95% CI = 0.85, 0.92) at 26 weeks (11% of patients with PAH deterioration, 248 patients at risk) to 56% (95% CI = 0.42, 0.67) at 234 weeks, at which time 93 patients (33%) experienced PAH deterioration (1 patient at risk).

A total of 40 deaths occurred during LVGX Part 2. Another death occurred within the 30-day reporting period after study drug discontinuation. The most frequent causes of death were cardiac failure, right ventricular failure, and respiratory failure. Three patients died due to worsening of PAH. One death was considered by the investigator to be due to the study drug; this death was caused by cardio-respiratory arrest.

A total of 134 patients (47%) experienced 372 SAEs. The most frequent SAEs were worsening of PAH and right ventricular failure. A total of 11 SAEs were considered by the investigator as possibly related to tadalafil treatment. No pregnancies were reported.

A total of 51 patients (18%) experienced 29 AEs that resulted in study discontinuation. Forty of these discontinuations were due to death, and the remaining 11 were from other AEs. The most frequent of the events causing discontinuation (including discontinuation due to death) were right ventricular failure (8 patients, 3%) and worsening PAH (5 patients, 2%). Three events that caused discontinuation were considered by the investigator to be related to study drug (1 patient each): cardiorespiratory arrest, pain in extremity, and lacrimation increased.

Of the 286 patients who took at least 1 dose of tadalafil in LVGX Part 2, 264 (92%) experienced at least 1 TEAE. Of the 286 patients, 106 (37%) experienced TEAEs that were considered by the investigator to be related to treatment.

The most frequent TEAEs were headache (56 patients, 20%) and diarrhea and nasopharyngitis (46 and 45 patients, respectively, 16%). The most frequent severe TEAEs were worsening of PAH (16 patients, 6%) and right ventricular failure (14 patients, 5%).

Overall, similar proportions of patients <65 years of age (92%) and ≥65 years of age (94%) experienced TEAEs; the overall AE profiles in these age groups were similar to that seen for all patients. Overall, a higher proportion of female patients (95%) than male patients (83%) experienced at least one TEAE; the overall AE profiles in these groups were similar to that seen for all patients.

Seventy-six patients (27%) reported treatment-emergent bleeding events. The most common bleeding events were epistaxis (21 patients, 7%), contusion (11 patients, 4%), and menorrhagia (8 patients, 3%). All events of vaginal hemorrhage and menorrhagia were of mild or moderate severity, and none of the events resulted in discontinuation from the study.

A total of 64 patients (22%) received at least 1 unique new PAH therapy during LVGX Part 2. The most common type of PAH therapies taken were prostacyclin or its analogue (36 patients, 13%) and endothelin receptor antagonist (35 patients, 12%).

Fewer bosentan users (20%) than non-users (26%) received at least 1 new PAH therapy during LVGX Part 2.

Conclusions: The long-term safety observed in patients with PAH in this study was as expected in this patient population treated with tadalafil. The continued administration of tadalafil to patients with PAH did not appear to negatively impact the safety of these patients or their survival.