

Summary ID# 10245

Clinical Study Summary: Study B4G-MC-B001

Observational Study to Determine the Incidence of New-Onset Cardiac Valvulopathy in Patients Treated with Pergolide as Second-Line Therapy for Parkinson's Disease

Date summary approved by Lilly: 09 July 2008

Title of Study: Observational Study to Determine the Incidence of New-Onset Cardiac Valvulopathy in Patients Treated with Pergolide as Second-Line Therapy for Parkinson's Disease.	
Investigator(s): This multicenter study included 8 principal investigator(s).	
Study Center(s): This study was conducted at 8 study center(s) in 4 countries.	
Publication(s) Based on the Study: None at this time.	
<p>Length of Study: Study was planned to last 30 months (3 follow-up echocardiograms at least every 6 to 12 months + long term follow-up period for 12 months). Date first patient enrolled: 22 March 2006 Date last patient completed: No patients completed the study as the study was terminated early per Sponsor recommendation and in agreement with the Pharmacovigilance Working Party of the Committee for Medicinal Products for Human Use (CHMP, PhVWP). Date study terminated: 24 May 2007</p>	<p>Phase of Development: IV (observational study)</p>
<p>Objectives:</p> <ul style="list-style-type: none"> • Primary objective: to estimate the incidence of new-onset valvulopathy, as determined by echocardiography-detected valvulofibrotic changes with evidence of valvular regurgitation relative to normal baseline or previous follow-up echocardiograms. • Secondary objective: to estimate the prevalence of valvulopathy, as determined by baseline echocardiograms, among all patients. 	
Study Design: Non-interventional observational study, phase IV, over a period of approximately	

30 months, patients treated with pergolide in accordance with recommendations listed in the appropriate country-specific Summary of Product Characteristics (SPC) as second-line therapy for Parkinson's disease (PD).
<p>Number of Patients:</p> <p>Planned: 500 entered and 200 enrolled patients in approximately 12 European Union countries.</p> <p>Entered: 34 patients, Enrolled: 28 patients.</p> <p>Completed: No patients completed.</p>
<p>Diagnosis and Main Criteria for Inclusion: Patients diagnosed with PD who were to receive pergolide as second-line therapy, either as monotherapy or as adjunctive therapy to levodopa, male or female, at least 18 years of age.</p>
<p>Test Product, Dose, and Mode of Administration: Pergolide mesylate given orally in accordance with dose recommendations listed in the appropriate country-specific SPC.</p>
<p>Duration of Treatment: The duration of treatment by pergolide was to be in accordance with the appropriate country-specific SPC.</p>
<p>Variables:</p> <p><u>Primary Outcome:</u> Incidence of new-onset valvulopathy.</p> <p><u>Secondary Outcome:</u> Prevalence of valvulopathy.</p> <p><u>Safety:</u> Cardiac Events related to valvulopathy</p> <p style="padding-left: 40px;">Vital Signs (that was, pulse rate, systolic blood pressure, diastolic blood pressure and weight),</p> <p style="padding-left: 40px;">Echocardiograms,</p> <p>Physical Examination.</p>
<p>Methods:</p> <p><u>Statistical:</u> - The incidence of new-onset valvulopathy was to be calculated as the number of patients with valvulopathy (as determined by the adjudication committee (AC)) in any of the 3 follow-up echocardiograms divided by the total number of patients without valvulopathy at baseline (also determined by the AC) and who had at least 1 follow-up echocardiogram while on pergolide therapy.</p> <p style="padding-left: 40px;">- The prevalence of valvulopathy was to be calculated as the number of patients with valvulopathy at the baseline echocardiogram, (as determined by the AC), divided by the total number of patients who entered the study prospectively.</p> <p>Regarding primary and secondary outcomes, Blaker's exact 95% confidence interval (CI) for a single proportion was to be computed.</p> <p>Assuming a valvulopathy incidence of 5% among study patients, study completion by 200 patients would have enabled the estimation of a 95% CI of 2.56% to 8.83%.</p>

Summary:

Patient Demographics and Characteristics

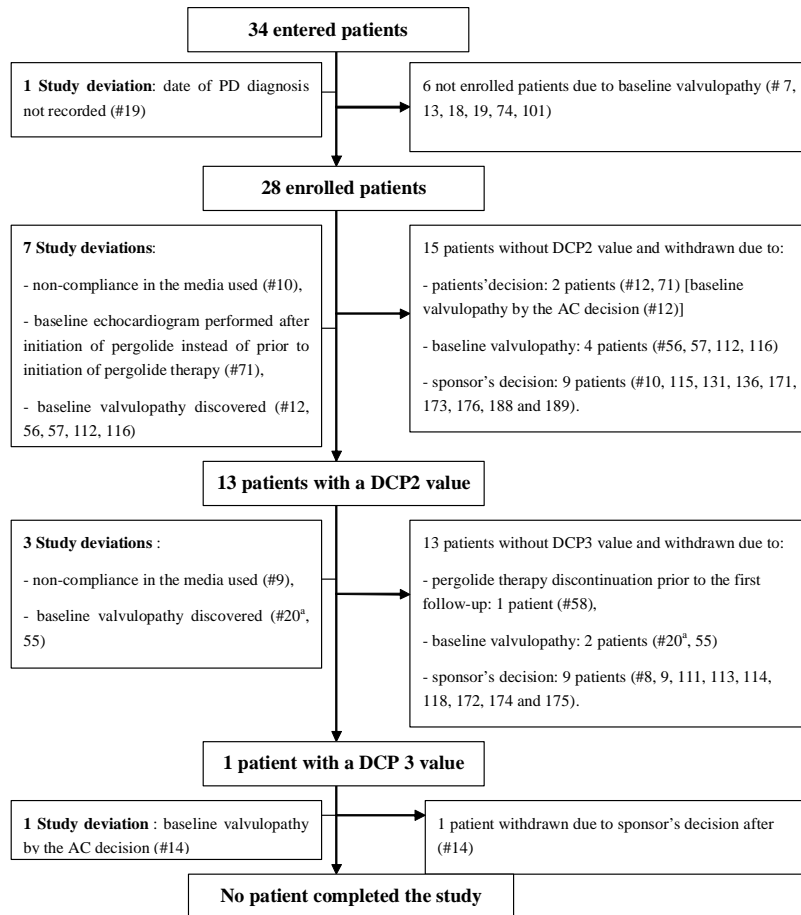
Of the 34 patients who entered the study, 28 were enrolled and no patients completed the study. Among the 34 entered patients, 6 patients (17.6%) discontinued the study prior to enrollment as they showed baseline cardiac valvulopathies.

All 28 patients who were enrolled discontinued the study. The most common reason for discontinuation was Sponsor decision (19 patients, 67.9%) (patients with a withdrawal reason of Sponsor decision and a termination date on or after 24 May 2007 were withdrawn due to study termination), followed by 6 patients (21.4%) who had a baseline

valvulopathy detected by a baseline echocardiogram performed by their local cardiologists, and who were incorrectly enrolled. Of the remaining 3 patients, 2 (7.1%) were withdrawn from the study due to their own decision, (one of these was later found to have baseline valvulopathy by AC), and 1 (3.6%) was withdrawn due to pergolide therapy discontinuation prior to the first follow-up.

No patients were withdrawn due to death or adverse event.

The disposition of patients is displayed in Figure B001.6.1 below.



^a This patient (#20) was enrolled with a non-significant baseline valvulopathy and discontinued later.

Abbreviations: DCP = Data Collection Points (Points in the study at which data were collected. They coincided with study entry and follow-up echocardiograms).

Figure B001.1. Disposition of patients, Observational Study B4G-MC-B001.

Due to the small number of patients enrolled, the patient characteristics are provided for all entered patients (n=34). The majority of patients were male (55.9%), Caucasian (97.1%), with a mean age of 62.3 ± 9.1 years and with a mean body mass index (BMI) of 27.0 ± 5.0 kg/m² (Table B001.1). The mean duration of PD before inclusion was 6.5 ± 6.1 years (range: 0.2 - 25.2) (Table B001.2).

**Table B001.1. Patient Demographics at Baseline
Observational Study All Patients**

	Total N=34
Gender	
Male	19 (55.9 %)
Female	15 (44.1 %)
Total	34 (100.0 %)
Age (years)	
Mean (SD)	62.3 (9.1)
95% CI	[59.1 ; 65.5]
Median	62.5
Range	39.0 - 76.0
Race	
Caucasian	33 (97.1 %)
African	0 (0.0 %)
Hispanic	0 (0.0 %)
Asian	1 (2.9 %)
Other	0 (0.0 %)
Total	34 (100.0 %)
BMI	
Mean (SD)	27.0 (5.0)
95% CI	[25.3 ; 28.8]
Median	25.9
Range	19.8 - 42.1
N Missing	1

Abbreviations: BMI=body mass index; CI=confidence interval; N=number; SD=standard deviation.

**Table B001.6.1 Summary of PD history at Baseline
Observational Study
All Patients**

Duration of PD (Years)	Total N=34
Mean (SD)	6.5 (6.1)
95% CI	[4.4 ; 8.7]
Median	4.1
Range	0.2 - 25.2
N Missing	1

Abbreviations: CI=confidence interval; N=number; PD= Parkinson's disease; SD=standard deviation

Primary Outcomes

The protocol and statistical analysis planned stipulated that the primary and secondary treatment outcomes of new-onset valvulopathy and prevalence of valvulopathy were to be based on echocardiograms reviewed by the AC. Six echocardiograms, all collected at DCP1 (baseline), were reviewed by the AC. The remaining echocardiograms were evaluated by the investigators, who provided their assessment of valvulopathy.

The incidence of new-onset valvulopathy was not estimated due to the fact that none of the follow-up echocardiograms were reviewed by the adjudication committee. Thirteen (46.4%) of the 28 enrolled patients had at least a data collection point 2 (DCP2) value. No patients completed the study due to the Sponsor's decision to terminate the study

Of the 28 enrolled patients, 1 patient (3.6%) was reported to have developed new onset valvulopathy during the course of the study based on investigator opinion. None of the echocardiograms for this patient were reviewed by the adjudication committee. Upon review of the cardiologist's report, Lilly does not concur that this is a new-onset valvulopathy. This patient had a PD history of 2.7 years, while he had no cardiovascular medical history and no cardiovascular family history.

The number of patients with DCP1 echocardiograms reviewed by the AC was insufficient to appropriately calculate the prevalence of valvulopathy among all patients being considered for pergolide treatment. Of the 34 entered patients, only 6 of the DCP1 echocardiograms were reviewed by the AC.

Regarding all entered patients (n = 34), 20 of them showed signs of cardiac valvulopathy at baseline: 14 patients had a pre-existing valvulopathy determined either by the AC or the investigator and 6 patients experienced baseline regurgitation (mainly mild aortic). Of these 14 patients, 8 were female, aged 44 to 76 years. Four of these patients previously took ergot derivatives. All of them had evidence of valvular regurgitation, mainly mitral and aortic and of a mild severity.

Safety

The range of treatment duration was 2.0 to 126.0 days. The daily doses of pergolide varied from 0.05 once daily (QD) to a maximum dose of 5 mg taken in 5 separate doses daily.

There were no serious cardiac adverse events (SAEs) or deaths reported during the study. No patient discontinued because of a cardiac adverse event related to treatment emergent valvulopathy.

Some adverse events were pre-existing at baseline and were not considered as treatment emergent. A total of 16 adverse events (AEs) occurred in the 6 entered patients who were not enrolled in the study. These AEs mainly belonged to cardiac disorders (14 AEs), followed by respiratory disorders (2 AEs).

From 28 enrolled patients, a total of 4 patients (14.3%) experienced a total of 7 treatment-emergent adverse events (TEAEs): 6 cardiac and 1 respiratory disorder. All but one (non-serious mitral valvulopathy) were considered as not related to pergolide treatment.

Of the 20 correctly enrolled patients (i.e. excluding the 8 enrolled patients with baseline valvulopathy), 1 patient (0.05%) experienced 4 TEAEs related to cardiac and respiratory disorders: two cases of sclerosis in mitral and aortic valves, one case of insufficiency in aortic valve and one case of dyspnoea. The relationship to the use of pergolide was pointed out in none of these.

No patients discontinued due to an adverse event.

Regarding pulse rate, systolic blood pressure (SBP) and diastolic blood pressure (DBP) in patients with a DCP2 value (13 patients): no significant change was observed in enrolled patients from baseline to DCP2.

Regarding physical examination, 1 patient showed abnormal dyspnea at study entry. No change was observed in enrolled patients with a DCP2 value (13 patients) from baseline to DCP2.

As this study was prematurely ended with insufficient data, no new conclusions relative to the safety of the pergolide treatment could be made. However, among entered patients, the percentage of patients with baseline valvulopathy appeared to be high (41.2%). All of them had evidence of valvular regurgitation, mainly mitral and aortic and of a mild severity.