FINAL CLINICAL STUDY REPORT

Study Title:	A Randomized, Double-blind, Placebo-controlled Study of Ranolazine in Patients with Heart Failure with Preserved Ejection Fraction
Name of Test Drug:	Ranolazine
Dose and Formulation:	Ranolazine ER (extended release) 1000 mg (two 500 mg tablets per dose) twice daily
Indication:	Heart Failure with Preserved Ejection Fraction
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-270-0101
Phase of Development:	Phase 2
IND No.:	Not applicable
EudraCT No.:	2009-017168-17
Study Start Date:	28 April 2010 (First Patient Screened)
Study End Date	08 February 2011 (Last Patient Contact)
Principal or Coordinating Investigator:	Name: Prof. Lars S. Maier, MD Affiliation: [redacted] [redacted] PPD
Gilead Responsible Medical Monitor:	Name: Beth Layug, MD Telephone: [redacted] PPD Fax: [redacted] PPD
Report Date:	16 September 2011

STUDY SYNOPSIS

Study GS-US-270-0101
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404 USA

Title of Study: Study GS-US-270-0101: A Randomized, Double-blind, Placebo-controlled Study of Ranolazine in Patients with Heart Failure with Preserved Ejection Fraction

Investigators: Professor Lars S. Maier, MD

Study Centers: [redacted] PPD

Publications: Planned

Study Period:

28 April 2010 (First patient screened)
08 February 2011 (Last patient contact)

Phase of Development: Phase 2

Objectives:

The primary objective of this study was to determine if ranolazine, compared to placebo, was effective in improving diastolic function in patients with heart failure with preserved ejection fraction (HFpEF).

Methodology: This was a single-center, randomized, double-blind, placebo-controlled proof-of-concept study of ranolazine in patients with HFpEF scheduled to undergo cardiac catheterization as part of a routine diagnostic procedure for standard of care. Patients were randomized in a 1.5:1 ratio to receive ranolazine or placebo. Treatment consisted of two loading intravenous (IV) bolus doses of study drug followed by a 24-hour infusion of study drug; one hour prior to completion of the infusion, patients started oral study drug (1000 mg twice daily) that continued until the end of the study on Day 14.

At screening (the day prior to cardiac catheterization), patients underwent the following procedures: tissue Doppler (TD) echocardiography, cardiopulmonary exercise test (CPET), and determination of N-terminal pro-brain B-type natriuretic peptide (NT-pro-BNP) concentration. During cardiac catheterization, left ventricular (LV) pressures and hemodynamic data were measured 3 times under resting conditions. The right atrium was then paced at 120 beats/min and the same measurements were repeated 3 times. If the average resting LV end-diastolic pressure (LVEDP) at rest was ≥ 18 mm Hg and the average resting time constant of relaxation (tau) was ≥ 50 msec, patients met continuing eligibility criteria and received study drug.

Left ventricular pressures and hemodynamic data at resting and paced conditions were repeated 30 minutes after initiation of study drug. Tissue Doppler echocardiography was repeated 22 hours after initiation of study drug. Patients remained in the clinic according to routine practice until discharge. On Day 14 (end of study) patients returned to the clinic and TD echocardiography, CPET, and NT-pro-BNP measurements were repeated.

Number of Subjects (Planned and Analyzed):

Planned: 20 patients

Analyzed: 20 patients received study drug (8 placebo, 12 ranolazine), and all 20 were included in the full analysis set, the pharmacokinetic analysis set, and the safety analysis set. One patient, randomized to ranolazine treatment, appropriately received ranolazine IV but erroneously received placebo tablets. The patient's data was included for all safety analyses and for the efficacy analyses only at the 30-minute and 22-hour time points.

Diagnosis and Main Criteria for Inclusion:

Eligible patients provided signed informed consent, were males or females, aged ≥ 40 years, with clinical symptoms of heart failure (New York Heart Association [NYHA] class II-III) at the time of screening (eg, dyspnea, paroxysmal nocturnal dyspnea, orthopnea, bilateral lower extremity edema). Patients were to have a left ventricular ejection fraction (LVEF) ≥ 45% at screening, with

- A mitral E wave velocity/mitral annular velocity ratio (E/E′) > 15 measured by TD echocardiography at screening,
  or
- NT-pro-BNP > 220 pg/mL at screening,
  and
- Average resting LVEDP ≥ 18 mm Hg at the time of cardiac catheterization
- Average resting tau ≥ 50 msec at the time of cardiac catheterization

In addition, female patients were to be postmenopausal (no menses for last 24 months) or sterilized or if of child-bearing potential, were not breastfeeding, had a negative pregnancy test at time of study, had no intention of becoming pregnant during the course of the study, and using one or more of the protocol-specified contraceptives.

Duration of Treatment: Patients received ranolazine or matching placebo for a total of 14 ± 2 days. Treatment began on Day 1 with two loading bolus IV injections of study drug, administered 15 minutes apart (at T=0 and T=15 minutes); at T=20 minutes, a continuous infusion was started and maintained for 24 hours. One hour prior to the end of the 24-hour infusion, patients were started on oral study drug that was continued until the end of the study (on Day 14).

Test Product, Dose, Mode of Administration, and Batch No.: Patients randomized to ranolazine treatment received two 92 mg doses by IV bolus of ranolazine injection; each bolus dose consisted of 10 mL of a 9.2 mg/mL ranolazine loading solution and was administered over 2 minutes followed by a saline flush (5 mL of 0.9% w/v saline). The bolus doses were followed by a continuous infusion of ranolazine, which was prepared at a concentration of 4 mg/mL and administered at a rate of 23 mL/h to deliver 92 mg/h. Oral ranolazine (supplied as tablets and administered at a dose of 1000 mg twice daily) was started one hour prior to completion of the 24-hour infusion and continued through the end of the study (Day 14).

Ranolazine injection (lot #905023) was supplied as a 25 mg/mL solution and diluted with saline by the pharmacist, as appropriate.

Ranolazine extended release (ER) 500 mg tablets had a bulk lot number of BW0901B1 and a blinded lot number of 270-0101/02.

Reference Therapy, Dose, Mode of Administration, and Batch No.: Patients randomized to placebo received two IV bolus injections of saline, followed by a continuous 24-hour infusion of saline. Oral placebo tablets (matching ranolazine ER tablets) were started one hour prior to completion of the 24-hour infusion and continued through Day 14.

Commercially available saline solution for the bolus injections and 24-hour infusion was supplied by the study site. The batch numbers of saline solution included: 09J30D and 10E03B (manufactured by [redacted]), 9502-1 (manufactured [redacted]), and 0215A192 and 0366A191 (manufactured by [redacted]).

Placebo tablets had a bulk lot number of BW0902B1 and a blinded lot number of 270-0101/02.

Criteria for Evaluation:

Efficacy: Efficacy was evaluated through the following exploratory endpoints:

1. Change from baseline to 30 minutes from initiation of the first bolus of study drug (T=30 min) in cardiac catheterization hemodynamic parameters (of tau, LVEDP, and the minimum rate of LV pressure change [dP/dt_{min}]) at both resting and paced conditions
2. Change from baseline to Day 14 in the following: E/E′ ratio, assessed by TD echocardiography; maximal oxygen uptake (VO_2 max), assessed by CPET; and NT-pro-BNP

Pharmacokinetics: Pharmacokinetic (PK) evaluations included: plasma concentrations of ranolazine during IV dosing, the observed minimum ranolazine plasma concentration (C_{min}), the observed maximum plasma concentration (C_{max}), and the time of C_{max} (T_{max}).

Safety: Safety was assessed through adverse events (AEs), serious AEs (SAEs), clinical laboratory tests (hematology, serum chemistry), physical examination, electrocardiography (ECG), and vital signs.

Statistical Methods:

Descriptive summaries included counts and percentages for categorical variables and sample size, mean, standard deviation (SD), minimum, median, and maximum values for continuous variables by treatment group.

Efficacy: Efficacy endpoints were summarized descriptively for the full analysis set (FAS) at baseline and for changes from baseline at schedule time points. The FAS included all patients who received at least one dose of study drug with at least one postbaseline primary efficacy measurement. A Wilcoxon rank sum test was used to analyze the endpoints between treatment groups.

Pharmacokinetics: The PK analysis set included all patients in the FAS who had evaluable PK concentrations at the time point of interest. Plasma concentrations of ranolazine were summarized with descriptive statistics (including mean, median, SD, coefficient of variation [% CV], minimum, and maximum). Plasma concentration-time data were analyzed by noncompartmental analysis using Phoenix WinNonlin 6.1, and C_{max}, C_{min}, and T_{max} were determined and summarized with descriptive statistics (including sample size, mean, SD, minimum, median, geometric mean, maximum, and % CV). The PK parameters in this study may not represent their true values since full plasma concentration-time profiles for ranolazine were not planned or obtained.

Safety: All safety data were summarized for the safety analysis set, which included all patients who received at least one dose of study drug. Adverse events were summarized (number and percentage of patients) by treatment group. Laboratory assessments, body weight, vital signs, and ECG results were summarized using descriptive statistics (sample size, mean, SD, median, first quartile [Q1], third quartile [Q3], minimum, and maximum).

SUMMARY – RESULTS:

Subject Disposition and Demographics: A total of 25 patients with HFpEF were randomized prior to cardiac catheterization; 5 patients did not proceed to treatment with study drug and were terminated from study participation due to failure to satisfy the continued eligibility criteria (3 patients) or investigator discretion (2 patients). The remaining 20 patients received study drug (8 placebo, 12 ranolazine) and completed the study. Overall, patients had a median age of 71.5 years, were predominantly female (75% placebo, 83% ranolazine), and all were white. All patients had a history of congestive heart failure, characterized as NYHA class II (37.5% placebo, 41.7% ranolazine) or class III (62.5% placebo, 58.3% ranolazine), and all patients had a history of hypertension. Concomitant medications most frequently included angiotensin converting enzyme inhibitors, beta blocking agents (selective), and platelet aggregation inhibitors.

Efficacy Results: Left ventricular hemodynamic and pressure measurements collected during cardiac catheterization showed that ranolazine-treated patients had statistically significant decreases in resting LVEDP (−2.13 ± 3.961 mm Hg; p=0.042), resting pulmonary capillary wedge pressure (PCWP; −2.08 ± 3.166 mm Hg; p=0.044), and mean pulmonary artery pressure (PAP) under paced conditions (−1.76 ± 2.381 mm Hg; p=0.016). There were no significant effects on other hemodynamic parameters including relaxation kinetics.

Measurements collected during CPET showed that after 2 weeks of oral treatment, the ranolazine group had a significant increase in the respiratory exchange ratio (RER; summarized as the difference between resting and exercise RER from baseline to Day 14: 0.09 ± 0.119; p=0.025), and a numeric decrease in the ventilation/carbon dioxide production ratio (V_E/VCO_2) (ie, the change from baseline in the difference between resting and exercise values for V_E/VCO_2 at Day 14: −2 ± 7.2) that was significantly lower than the placebo group (p=0.034). The ranolazine-treated group had numerically increased exercise duration of 55 seconds compared to 38 seconds for the placebo group (p=0.866).

There were no significant effects on echocardiographic parameters or NT-pro-BNP.

Pharmacokinetic Results: Ranolazine plasma concentrations for the 12 ranolazine-dosed patients (measured during IV dosing only) were 1610 ng/mL (at 10 minutes), 4036 ng/mL (at 20 minutes), 3109 ng/mL (at 30 minutes), and 10173 ng/mL (at 22 hours). At the 22-hour time point, one patient had an improbably high ranolazine plasma concentration of 63000 ng/mL. Excluding this high value, the mean plasma concentration at 22 hours for the remaining 11 patients was 4910 ng/mL. Based on the concentration-time data, average values for C_{min}, C_{max}, and T_{max} were 1610 ng/mL, 5595 ng/mL, and 22 hours, respectively.

Safety Results: Adverse events were experienced by 87.5% of patients in the placebo group and 83.3% of patients in the ranolazine group. Adverse events reported for at least 2 of the 20 patients who received study drug (ie, placebo or ranolazine) included constipation, vertigo, haematoma, nausea, back pain, hypotension, and headache. The proportion of patients with constipation was notably higher in the ranolazine group than in the placebo group (0% placebo, 58% ranolazine); constipation was also most frequently considered by the investigator as related to study drug. Four patients (1 placebo, 3 ranolazine) had an AE graded as severe; for 3 of these patients (all in the ranolazine group), a total of 5 SAEs were reported, as follows: retroperitoneal haematoma, vascular pseudoaneurysm, muscle haemorrhage, haemoptysis, and musculoskeletal chest pain. None of the SAEs were considered by the investigator as related to study drug, but for 2 patients, the SAEs were considered related to study procedures. There were no deaths and no patient discontinued from the study due to an AE.

Changes in ECG intervals were larger for patients treated with ranolazine than placebo. One patient (with first degree AV block and a PR interval of 220 msec at screening) had an increase in the QRS complex from 88 msec at screening to 96 msec following ranolazine dosing that the investigator considered to be clinically significant; this finding was also reported as a mild, drug related AE. No other patient had a clinically significant ECG finding, and no patient had a ventricular arrythmia or torsades de pointes. There were no clinically significant changes in laboratory assessments, vital signs, or physical examinations.

CONCLUSIONS: The results of this exploratory study showed that ranolazine treatment improved some measures of diastolic dysfunction, with decreases in resting LVEDP, resting PCWP, and mean PAP under paced conditions. Measurements collected during CPET showed that after 2 weeks of treatment, the ranolazine group had a significant increase in RER compared to baseline values and a significant decrease in V_E/VCO_2 compared to the placebo group. Exercise duration also increased numerically in the ranolazine-treated group. There were no significant effects on echocardiographic parameters or NT-pro-BNP.

The proportion of patients with AEs in the ranolazine group was similar to that in the placebo group. Serious AEs were only reported for ranolazine-treated patients, however, no SAE was considered related to study drug. Constipation was the most commonly reported AE, was reported only with ranolazine treatment, and was most frequently considered related to study drug.