2.0 SYNOPSIS

Name of Sponsor/Company: Forest Research Institute, Inc., a subsidiary of Forest Laboratories, Inc. Harborside Financial Center, Plaza V Jersey City, NJ 07311 Phenomix Corporation was the original IND holder and sponsor of this study. The IND was transferred from Phenomix to Forest on 15 July 2009.	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of Finished Product: Not applicable	**Volume:**	
Name of Active Ingredient: dutogliptin/PHX1149T	**Page:**	

Study Number: PHX1149-PROT302

Title of Study: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study to Evaluate Safety and Efficacy of Dutogliptin/PHX1149T in Subjects With Type 2 Diabetes Mellitus on a Background Medication of Metformin.

Investigator(s): Multicenter study; a complete list of Investigators is provided in Appendix 16.1.4.

Study Center(s):
96 study centers: 34 in the United States, 14 in Poland, 12 in Argentina, 12 in India, 11 in Peru, 9 in Czech, and 4 in Chile.

Publication (reference): Not applicable.

Study Period: First Patient First Visit: 27-Apr-2009 Last Patient Last Visit: 03-Aug-2010 Early Termination Date of Study: 26-Jun-2010	**Development Phase:** 3

Objectives: The primary objective of this study was to demonstrate the efficacy of dutogliptin over 26 weeks, as evidenced by placebo-corrected changes in glycosylated hemoglobin (HbA_{1c}) relative to baseline. The secondary objectives were to demonstrate safety and tolerability of dutogliptin and to demonstrate changes in fasting plasma glucose over 26 weeks.

Study Design: This was a randomized, double-blind, placebo-controlled, multicenter, parallel-group study with a screening period of up to 3 weeks, a 4-week single-blind, placebo run-in period, and a 26-week double-blind (DB) treatment period. Patients who completed the placebo run-in period were randomized 1:1 to receive placebo or dutogliptin 400 mg once daily during the 26-week DB treatment period. Patients received background treatment with metformin with dutogliptin or placebo for 26 weeks. Patients meeting pre-specified criteria for inadequate control of T2DM were given rescue therapy. Patients who completed the 26-week DB treatment period (Visit 8) were offered access to an optional, DB, active-controlled extension study. This extension study (PHX1149-PROT402) is summarized in a separate report. Patients who did not wish to participate in the extension study had a safety visit (Visit 9) after stopping DB investigational product at Visit 8.

Diagnosis and Main Criteria for Inclusion: Adult male and female outpatients, 18-85 years of age, inclusive, who had been diagnosed with T2DM at least 4 months before the Screening Visit (Visit 1), with a body mass index of 20 to 48 kg/m^2, inclusive; an HbA_{1c} level of 7.0% to 10.0%, inclusive; and a fasting plasma C-peptide greater than 0.26 nmol/L (or > 0.8 ng/mL) at the Screening Visit were eligible for enrollment. Patients needed to be on treatment with a stable dose of metformin of ≥ 2000 mg (or highest tolerated dose) used in accordance with product labeling for at least 6 weeks prior to screening. At randomization (Visit 4), patients had to have an HbA_{1c} level ≥ 7.0% and ≤ 10% value obtained at Visit 3. Patients with type 1 diabetes mellitus were not eligible for the study.

Number of Patients:

	Placebo	*Dutogliptin 400 mg*	*Total*
Total number of patients screened = 1267			
Randomized, N	**367**	**372**	**739**
Safety, N	**366**	**371**	**737**

The Screened Population consisted of all patients who underwent the Screening Visit and received a patient identification number.
The Randomized Population consisted of all patients in the Screened Population who were randomized to a treatment group in the study.

The Safety Population consisted of all patients in the Randomized Population who took at least 1 dose of double-blind investigational product (IP).

Investigational Product, Dose and Mode of Administration, Batch Number: Dutogliptin tablets 400 mg, 1 tablet/day, oral administration, [redacted]

Reference Therapy, Dose and Mode of Administration, Batch Number: Matching Placebo tablets, 1 tablet/day, oral administration, lots [redacted]

Duration of Treatment: 30 weeks, to include a 4-week single-blind placebo run-in period, followed by 26 weeks of DB treatment.

Criteria for Evaluation:
Efficacy: The efficacy evaluations listed below were planned but the analysis was not performed because the study was terminated early by the Sponsor for business reasons.

Primary: Change in HbA_{1c}, from baseline at Week 26/Visit 8 (last observation carried forward [LOCF]).
Secondary:
- Change in fasting plasma glucose from baseline at Week 26/Visit 8 (LOCF).
- Percentage of patients reaching treatment goal of $HbA_{1c} < 7\%$ at Week 26/Visit 8 (LOCF).

Additional:
- Change from baseline in HbA_{1c} at each postbaseline visit.
- Change from baseline in fasting plasma glucose at each postbaseline visit.

Safety: Adverse event (AE) recording, clinical laboratory parameters, vital signs (temperature, pulse, respirations, and blood pressure), body weight, electrocardiograms (ECGs), and targeted physical examination findings.

Pharmacokinetics/Pharmacodynamics: The pharmacokinetic and pharmacodynamic analyses listed below were planned for all patients in the study:
- Plasma dutogliptin levels before IP dosing and at 30 minutes (± 10 minutes) and 2 hours (± 10 minutes) after IP dosing at baseline (Visit 4) and predose and at 7 hours (± 1 hour) after IP dosing at Visits 6 and 8.
- Assessment of percent ex vivo dipeptidyl peptidase type 4 inhibition before IP dosing and at 30 minutes (± 10 minutes) and 2 hours (± 10 minutes) after IP dosing at baseline (Visit 4) and predose and at 7 hours (± 1 hour) after IP dosing at Visits 6 and 8.

Statistical Methods:
Efficacy: As planned, efficacy analyses would be performed based on the Intent-to-Treat (ITT) Population. The ITT Population was defined as all patients in the Safety Population with at least one postbaseline assessment of HbA_{1c}. The primary efficacy parameter was the change in HbA_{1c} from baseline at Visit 8 (LOCF). Between-treatment group differences for this parameter would be analyzed using an analysis-of-covariance model with treatment group and country as factors and the baseline in HbA_{1c} as a covariate.

However, efficacy analyses were not performed because the study was terminated early by the Sponsor for business reasons.

Safety: The safety parameters, which were summarized descriptively on the Safety Population, included AEs, clinical laboratory parameters, vital sign measurements, body weight, and ECG parameters. For each parameter, the last assessment made before the first dose of DB IP was used as the baseline for all analyses of that parameter.

Pharmacokinetic/Pharmacodynamic: Analyses were not performed because the study was terminated early by the Sponsor for business reasons.

SUMMARY OF RESULTS:

Disposition: There were 1267 patients who were screened in the study. Of the 739 patients in the Randomized Population, 206 patients completed the study. "Decision of Sponsor" was the most common reason for study discontinuation (457 [61.8%], which includes 14 patients for whom the "Other" reason for premature discontinuation was reported as study terminated by Sponsor) (Table 10-1).

Demographics and Other Baseline Characteristics: The mean age of patients in the Safety Population was approximately 54.9 years. Slightly more than half of the patients were female (51.2%), Non-Hispanic or Non-Latino (50.9%), and Caucasian (62%). The mean body mass index of all patients in the Safety Population was 31.2 kg/m^2.

Efficacy Results: Planned efficacy analyses were not performed in the study.

Pharmacokinetic Results: Analyses were not performed because the study was terminated early by the Sponsor for business reasons.

Safety Results:

- No deaths were reported in the study.
- Treatment-emergent serious adverse events (SAEs) were reported in 16 patients (8 [2.2%] patients in the placebo group and 8 [2.2%] patients in the dutogliptin group). None of the SAEs were considered to be related to the IP.
- Adverse events resulting in premature discontinuation from the study were reported in 12 patients (7 [1.9%] patients in the placebo group and 5 [1.3%] patients in the dutogliptin group). Two of the events leading to discontinuation were also SAEs, cholecystitis, reported for 1 patient in the placebo group, and ischemic stroke, reported for 1 patient in the dutogliptin group.
- Overall, treatment-emergent adverse events (TEAEs) were reported for 160 (43.7%) patients in the placebo and 165 (44.5%) patients in the dutogliptin group. TEAEs reported in at least 3% of patients in the dutogliptin group were hypoglycemia (22 [5.9%] patients), urinary tract infection (17 [4.6%] patients), and upper respiratory tract infection (3 [0.8%] patients). Urinary tract infection was reported in a similar frequency in the placebo group (14 [3.8%]); hypoglycemia was reported in 5 (1.4%) patients and upper respiratory tract infection was reported in 13 (3.6%) patients in the placebo group.

CONCLUSIONS:

Study PHX1149-PROT302 was a Phase 3, randomized, DB, placebo-controlled, multicenter study to evaluate safety and efficacy of dutogliptin in patients with T2DM on a background medication of metformin.

Due to early termination of the study, there were not adequate data collected to perform meaningful efficacy analyses. Therefore, no efficacy analyses were performed.

Safety results showed that treatment was well tolerated. A similar percentage of patients in each treatment group reported TEAEs (43.7% placebo; 44.5% dutogliptin). There was a small number of treatment-emergent SAEs; the incidence was the same in the 2 treatment groups (2.2%). None of the SAEs were considered to be related to the IP. The only SAE, by preferred term, reported in more than 1 patient was cholecystitis (reported in 2 patients in the placebo group). The number of patients who discontinued after randomization due to AEs was similar in both groups (7 [1.9%] in the placebo group and 5 [1.3%] in the dutogliptin group.

Date of Report: 25-Mar-2011