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-PROT402

Title of Study: A Phase 3, Randomized, Double-Blind, Active-Controlled, Multi-Center Extension Study to Evaluate the Safety and Efficacy of Dutogliptin 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):
36 study centers: 23 in the United States, 5 in Poland, 4 in India, 3 in Argentina, 1 in Czech Republic.

Publication (reference): Not applicable.

Study Period: First Patient First Visit: 08-Dec-2009 Last Patient Last Visit: 28-Jun-2010 Early Termination Date of Study: 25-Jun-2010	**Development Phase:** 3

Objectives: The primary objective of this study was to demonstrate the safety and tolerability of dutogliptin. The secondary objectives were to demonstrate maintenance of lowering or further reduction of glycosylated hemoglobin (HbA_{1c}) and to demonstrate maintenance of lowering or further reduction of fasting plasma glucose.

Study Design: A multicenter, double-blind, sitagliptin-controlled, 52-week extension study to evaluate the safety and efficacy of dutogliptin in patients with Type 2 diabetes mellitus (T2DM) who completed dutogliptin Phase 3 core study PHX1149-PROT302. Patients who were previously randomized to placebo in PHX1149-PROT302 received sitagliptin 100 mg and dutogliptin-matched placebo in a blinded manner and patients previously randomized to dutogliptin in PHX1149-PROT302 received dutogliptin 400 mg and sitagliptin-matched placebo in a blinded manner in this study. Patients continued background therapy of metformin from the core study (and pioglitazone, if rescued during the core study) and additional antidiabetic drug(s) other than glucagon-like peptide-1 analogues and dipeptidyl peptidase type 4 inhibitors (other than study drug) was used if necessary.

Diagnosis and Main Criteria for Inclusion: Adult male and female outpatients who completed the double-blind treatment period of the core protocol (Visit 8/Day 210 of PHX1149-PROT 302).

Number of Patients:

	Sitagliptin 100 mg	**Dutogliptin 400 mg**	**Total**
Enrolled, N	**75**	**85**	**160**
Safety, N	**75**	**85**	**160**

The Enrolled Population consisted of all patients who completed the core study and were enrolled in this sitagliptin-controlled extension study.

The Safety Population consisted of all patients in the Enrolled Population who took at least 1 dose of extension investigational product.

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 Dutogliptin Placebo tablets, 1 tablet/day, oral administration, [redacted].
Sitagliptin capsule 100 mg (capsule containing two 50-mg tablets), oral administration, [redacted].

Matching Sitagliptin Placebo capsules, 1 capsule/day, oral administration, [redacted].

Duration of Treatment: 52 weeks (approximately 365 days)

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

- Change in HbA_{1c} and fasting plasma glucose from baseline (Visit 4 of PHX1149-PROT302) at each scheduled visit.

Safety
Adverse event (AE) recording, clinical laboratory parameters, vital signs (temperature, pulse, respirations, and blood pressure), body weight, electrocardiograms, and targeted physical examination findings. Electrocardiographic data were not available because of the early termination by the Sponsor for business reasons.

Pharmacokinetics/Pharmacodynamic Sampling
Not Applicable.

Statistical Methods:
Efficacy: As specified in the protocol, the efficacy analyses would have been performed based on the Intent-to-Treat (ITT) Population. The ITT Population was defined as all patients in the Safety Population with at least 1 post-Visit 8 assessment of HbA_{1c} or fasting plasma glucose. The efficacy parameters were the change in HbA_{1c} and fasting plasma glucose from baseline (Visit 4 of PHX1149-PROT302) at each scheduled visit. Efficacy variables were to be summarized by visit using descriptive statistics.

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, were AEs, clinical laboratory parameters, and vital sign measurements. Target physical examination findings were not summarized. For each parameter, the last assessment made before the first dose of double-blind investigational product (IP) in the core study (PHX1149-PROT302) was used as the baseline for all analyses of that parameter.

SUMMARY OF RESULTS:
Disposition: A total of 160 patients were enrolled in the study; all enrolled patients were included in the Safety Population. There were 75 patients in the sitagliptin group and 85 patients in the dutogliptin group. The mean duration of treatment was 105.5 days for patients in the sitagliptin group and 100.2 days for patients in the dutogliptin group. Of the 160 patients in the Safety Population, no patients completed the study. Decision of Sponsor was the most common reason for study discontinuation (145 [90.6%] patients, including 2 patients for whom the "other" reason for premature discontinuation was indicated as study terminated by Sponsor).

Demographics and Other Baseline Characteristics: The mean age of patients in the Safety Population was approximately 54.8 years. Slightly more patients were female (50.6%) and Non-Hispanic or Non-Latino (53.8%); most were Caucasian (86.3%). The mean body mass index of all patients in the Safety Population was 31.7 kg/m^2.

Efficacy Results: Efficacy analyses planned were not performed in the study.

Safety Results:
- No deaths were reported in the study.

- Treatment-emergent serious adverse events (SAEs) were reported in 2 patients: 1 SAE in 1 (1.3%) patient in the sitagliptin group and 1 SAE in 1 (1.2%) patient in the dutogliptin group. Neither treatment-emergent SAE was considered to be related to the IP.

- Adverse events resulting in premature discontinuation from the study were reported in 3 patients, all in the dutogliptin group. One event, atrial fibrillation, was considered serious.

- Overall, treatment-emergent adverse events (TEAEs) were reported for 25 (33.3%) patients in the sitagliptin group and 33 (38.8%) patients in the dutogliptin group. The only TEAE reported in at least 3% of the patients in the dutogliptin group was hypoglycemia (5 [5.9%] patients); hypoglycemia was reported in 1 (1.3%) patient in the sitagliptin group.
- Newly emergent adverse events occurred in 20 (26.7%) patients in the sitagliptin group and 24 (28.2%) patients in the dutogliptin group. The only NEAE reported in at least 3% of the patients in the dutogliptin group was hypoglycemia (4 [4.7%] patients); hypoglycemia was reported in 1 (1.3%) patient in the sitagliptin group.

CONCLUSIONS: Study PHX1149-PROT402 was a Phase 3, double-blind, multicenter, sitagliptin-controlled, 52-week extension study to evaluate safety and efficacy of dutogliptin in patients with T2DM on a background medication of metformin who completed the dutogliptin Phase 3 core study PHX1149-PROT302.

Due to early termination of the study, there were not adequate data collected to perform meaningful efficacy analyses. Therefore, no efficacy results are presented for this clinical study report.

Safety results showed that treatment was tolerated well by patients in both the sitagliptin and dutogliptin groups. A similar percentage of patients in each treatment group reported TEAEs (33.3%, sitagliptin; 38.8%, dutogliptin). There was only 1 SAE in each treatment group; neither SAE was considered to be related to the IP. The rate of discontinuation due to TEAEs was low; only 3 (1.9%) patients, all in the dutogliptin group, discontinued due to TEAEs. The incidence of hypoglycemia reported as a TEAE was low in both treatment groups, but higher in the dutogliptin group (5.9%) than the sitagliptin group (1.3%).

Date of Report: 8 Mar 2011