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-PROT306		
Title of Study: A Randomized, Double-Blind, Placebo- and Sitagliptin-Controlled, Multicenter Study to Evaluate Safety and Efficacy of Dutogliptin in Type 2 Diabetes Mellitus Subjects With Moderate and Severe Renal Impairment Including Subjects on Hemodialysis.		
Investigator(s): Multicenter study; a complete list of Investigators is provided in Appendix 16.1.4 of the clinical study report.		
Study Center(s): 34 study centers: 16 in the United States, 11 in Russia, and 7 in the Ukraine.		
Publication (reference): Not applicable.		
Study Period: First Patient First Visit: 25-Aug-2009 Last Patient Last Visit: 09-Feb-2010 Early Termination Date of Study: 03-Feb-2010	**Development Phase:** 3	
Objectives: The primary objective of this study was to assess the safety and tolerability of dutogliptin in patients with type 2 diabetes mellitus (T2DM) with moderate or severe renal impairment. The secondary objectives were to assess changes in glycosylated hemoglobin (HbA_{1c}) and fasting plasma glucose and to collect pharmacokinetic and pharmacodynamic (ex vivo inhibition of dipeptidyl peptidase type 4 [DPP4]) information on dutogliptin in a subset of patients.		

Study Design: This was a randomized, double-blind, placebo-controlled, multicenter, parallel-group study with a screening period of up to 3 weeks. The initial randomized, double-blind, placebo-controlled period of this trial was 26 weeks in duration. Approximately 180 patients with moderate renal impairment were to be randomized 2:1 to dutogliptin 200 mg once daily or placebo. Likewise, 180 patients with severe renal impairment (including hemodialysis patients at a subset of sites) were to be randomized 2:1 to dutogliptin 100 mg once daily or placebo. Patients on hemodialysis (N = 15) were to be enrolled only after completion of a separate pilot Phase 1 pharmacokinetic study in which safety and tolerability as well as the proposed dose reduction in this population had been confirmed. Renal impairment was determined by the Modification of Diet in Renal Disease (MDRD) formula in which a glomerular filtration rate (GFR) estimate of 30 to 59 mL/min/1.73 m^2 was the range for moderate renal impairment, and a GFR estimate < 30 mL/min/1.73 m^2 was the range for severe renal impairment. Randomization to active or placebo within the moderate and severe treatment groups were to be stratified by background medication and geographic region. Patients meeting pre-specified criteria for inadequate control of T2DM were to be given rescue therapy.

At the end of the double-blind, placebo-controlled period (Day 182), there was to be a 26-week double-blind sitagliptin-controlled period of the study in which all patients were to continue. Patients randomized to placebo in the double-blind, placebo-controlled period were to receive sitagliptin in a blinded manner in the sitagliptin-controlled period. Patients randomized to dutogliptin in the double-blind, placebo-controlled period were to continue on the same dose of dutogliptin in the sitagliptin-controlled period.

If renal impairment progressed from moderate to severe at any time during the study, the dose of dutogliptin was to be reduced to 100 mg once daily; an appropriate dose reduction for sitagliptin was to be made as well.

Diagnosis and Main Criteria for Inclusion: Adult male and non-pregnant (and not planning to become pregnant during the study), non-lactating female patients, 18-85 years of age, inclusive, who had been diagnosed with T2DM at least 4 months before the Screening Visit (Visit 1), with a HbA_{1c} level of 7.0% to 10.5%, inclusive; and renal impairment as determined by MDRD formula calculation of GFR estimate ≤ 59 mL/min/1.73m^2 at the Screening Visit (Visit 1) were eligible for enrollment. Patients on hemodialysis had to have stable renal status for at least 6 months before the Screening Visit (Visit 1), with a functional, mature, arteriovenous shunt. Patients may have been drug-treatment naive for antidiabetic drugs, or treated with any combination of a sulfonylurea, thiazolidinedione, meglitinide, acarbose, or insulin as background medications. Patients treated with metformin, glucagon-like peptide-1 analogues, or DPP4 inhibitors were not eligible for the study. Patients with type 1 diabetes mellitus or a history of diabetic ketoacidosis were not eligible for the study.

Number of Patients:

	Patients with Moderate Renal Impairment		***Patients with Severe Renal Impairment***	
	Placebo	*Dutogliptin 100 mg[a]*	*Placebo*	*Dutogliptin 200 mg[a]*
Total number of patients screened = 123				
Randomized, N[b]	**11**	**17**	**8**	**15**
Safety, N	**11**	**17**	**8**	**15**

The Screened Population consisted of all patients who underwent the Screening Visit and received a patient identification (PID) number.

The Randomized Population consisted of all patients in the Screened Population who were randomized to a double-blind 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).

a Due to a programming error in the interactive-voice- response system, the patients with moderate renal failure received dutogliptin 100 mg/day (the dose intended for patients with severe renal impairment) and patients with severe renal failure received dutogliptin 200 mg/day (the dose intended for patients with moderate renal impairment). Data are presented based on the actual programmed treatment allocation, not on treatment allocation per protocol.

b The planned number of patients to be randomized was approximately 360 patients. The target number of randomized patients (N = 360) was not reached because the study was terminated early by the Sponsor for operational reasons.

Investigational Product, Dose and Mode of Administration, Batch Number: Dutogliptin tablets 100 mg and 200 mg, 1 tablet/day, oral administration, [redacted].

Reference Therapy, Dose and Mode of Administration, Batch Number: Matching Placebo tablets, 1 tablet/day, oral administration, [redacted]. No sitagliptin was sent to the sites.

Duration of Treatment: 52 weeks, to include 26 weeks of double-blind, placebo-controlled treatment, followed by 26 weeks of double-blind, sitagliptin-controlled treatment.

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 operational reasons.

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

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

Pharmacokinetics/Pharmacodynamics: On Days 1 (Visit 2), 98 (Visit 5), and 182 (Visit 7), serial blood draws for plasma levels of dutogliptin and ex vivo DPP4 inhibition were to be performed in a subset of approximately 30 patients with moderate renal impairment and approximately 30 patients with severe renal impairment (of which approximately 15 patients were to have been on hemodialysis). In addition, in approximately 50% of all patients a trough pharmacokinetic/pharmacodynamic blood draw was to be performed on Days 98 (Visit 5) and 182 (Visit 7) only.

Statistical Methods:
Efficacy: As planned, the efficacy analyses would have been performed on all patients in the Intent-to-Treat (ITT) Population. The ITT Population consisted of all patients in the Safety Population who had at least one postbaseline assessment of HbA_{1c}. Change from baseline in HBA_{1c} and change from baseline in fasting plasma glucose were to be summarized using descriptive statistics and exploratory efficacy analyses were to be performed using an analysis of covariance model with treatment group and country as factors and the corresponding baseline value as a covariate.

Efficacy analyses were not performed because the study was terminated early by the Sponsor for operational reasons.

Safety: The safety parameters, except targeted physical examination findings and estimated GFR parameters, were AEs, clinical laboratory parameters, vital sign measurements, and ECG parameters, and were summarized descriptively on the Safety Population. For each parameter, the last assessment made before the first dose of double-blind IP was used as the baseline for all safety analyses of that parameter. Analyses are presented based on the actual treatment allocation, not on treatment allocation per protocol.

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

SUMMARY OF RESULTS:
Disposition: The target number of randomized patients (N = 360) was not reached because the study was terminated early by the Sponsor for operational reasons. PHX1149-PROT306 was suspended on 19 Nov 2009 because of a programming error in the interactive-voice-response system (IVRS) and the decision to terminate the study was made for operational reasons on 03 Feb 2010. Of the 51 patients in the Randomized Population, 28 patients had moderate renal impairment and 23 patients had severe renal impairment. No patient completed the study. Decision of Sponsor was the most common reason for study discontinuation for patients with moderate renal impairment (96.4%) and for patients with severe renal impairment (87.0%).

Demographics and Other Baseline Characteristics: Among the 28 patients in the Safety Population with moderate renal impairment, the mean age of patients was approximately 66.2 years. Most patients were male (57.1%), Non-Hispanic (96.4%), and Caucasian (71.4%). The mean body mass index of patients with moderate renal impairment in the Safety Population was 33.5 kg/m^2.

Among the 23 patients in the Safety Population with severe renal impairment, the mean age of patients was approximately 62.0 years. Most patients were female (52.2%), Non-Hispanic (69.6%), and Caucasian (73.9%). The mean body mass index of patients with severe renal impairment in the Safety Population was 34.2 kg/m^2.

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

Pharmacokinetic Results: Available pharmacokinetic data are presented in Appendix 16.8.2.

Safety Results:
One death was reported in the study. One patient with severe renal impairment who received dutogliptin 200 mg had SAEs of cellulitis, decreased appetite, acute hepatic failure, sepsis, respiratory distress, cardiac arrest, and cholecystitis that resulted in death.

Treatment-emergent SAEs were reported in 2 patients who received placebo and 1 patient who received dutogliptin 200 mg; all 3 patients had severe renal impairment. In addition, an SAE was reported during the screening period in 1 of these patients in the placebo group. None of the SAEs, by preferred term, were reported in more than 1 patient, and none were considered to be related to the IP.

Adverse events resulting in premature discontinuation from the study were reported in 2 patients; both patients had severe renal impairment and received dutogliptin 200 mg. Two AEs that led to discontinuation in 1 patient were considered to be related to the IP by the Investigator.

Among the 28 patients in the Safety Population with moderate renal impairment, TEAEs were reported in 11 patients: 4 (36.4%) patients received placebo and 7 (41.2%) patients received dutogliptin 100 mg. TEAEs reported in at least 2 moderate renal impairment patients were peripheral edema (reported in 2 patients who received dutogliptin 100 mg) and hypoglycemia (reported in 2 patients who received placebo and 1 patient who received dutogliptin 100 mg). All other TEAEs were reported in 1 patient each.

Among the 23 patients in the Safety Population with severe renal impairment, TEAEs were reported in 10 patients: 5 (62.5%) patients received placebo and 5 (33.3%) patients received dutogliptin 200 mg. TEAEs reported in at least 2 severe renal impairment patients were excoriation (reported in 1 patient who received placebo and 1 patient who received dutogliptin 200 mg), hypertensive crisis (reported in 1 patient who received placebo and 1 patient who received dutogliptin 200 mg), hypoglycemia (reported in 2 patients who received placebo), and urinary tract infection (reported in 1 patient who received placebo and 1 patient who received dutogliptin 200 mg). All other TEAEs were reported in 1 patient each.

CONCLUSIONS:
Study PHX1149-PROT306 was a Phase 3, randomized, double-blind, placebo-controlled, multicenter study to evaluate the safety and efficacy of dutogliptin in adult patients with T2DM with moderate or severe renal impairment.

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 with moderate or severe renal impairment. Among the patients with moderate renal impairment, the percentage of patients with reported TEAEs was similar in the treatment groups (36.4% placebo; 41.2% dutogliptin). Among the patients with severe renal impairment, TEAEs were reported in 62.5% of patients who received with placebo and 33.3% of patients who received dutogliptin 200 mg. One death was reported in the study in 1 patient with severe renal impairment who received dutogliptin 200 mg and had SAEs of cellulitis, decreased appetite, acute hepatic failure, sepsis, respiratory distress, cardiac arrest, and cholecystitis that resulted in death. There were a small number of patients with SAEs: 2 patients who received placebo and 1 patient who received dutogliptin; all 3 patients had severe renal impairment. None of the SAEs were considered to be related to the IP by the Investigator. Two patients discontinued prematurely due to AEs; both patients had severe renal impairment and received dutogliptin 200 mg. Two AEs that led to discontinuation were considered to be related to the IP by the Investigator. It is difficult to determine the contribution of the error in dosing to the safety profile of dutogliptin exhibited in this study.

Date of Report: 17-Mar-11