1.0 TITLE PAGE

Forest Research Institute, Inc.
Harborside Financial Center, Plaza V
Jersey City, NJ 07311

STUDY NUMBER: DUT-MD-304

Title: A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE SAFETY AND EFFICACY OF DUTOGLIPTIN IN PATIENTS WITH TYPE 2 DIABETES MELLITUS ON BACKGROUND TREATMENT WITH PIOGLITAZONE

Name of Investigational Product: Dutogliptin
Development Phase: 3
Indication Studied: Type 2 Diabetes Mellitus
Study Design: A randomized, double-blind, placebo-controlled, multicenter, parallel-group study with a screening period of up to 12-weeks, a 4-week single-blind placebo run-in period, and a 26-week double-blind treatment period.
First Patient, First Visit Date: 24-Aug-2009
Last Patient, Last Visit Date/Early Termination Date of Study: 05-Aug-2010/24-Jun-2010
Report Date: [Date final report sent for signature]

Sponsor's Chief Medical Officer: [redacted]

The study was carried out in compliance with ICH-E6 Good Clinical Practice.

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	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: DUT-MD-304		
Title of Study: A Phase III, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Safety and Efficacy of Dutogliptin in Patients With Type 2 Diabetes Mellitus on Background Treatment With Pioglitazone.		
Investigator(s): Multicenter study; a complete list of Investigators is provided in Appendix 16.1.4.		
Study Center(s): 129 study centers: 97 in the United States, 15 in India, 9 in Romania, 4 in Lithuania, 3 in Germany, and 1 in Colombia		
Publication (reference): Not applicable.		
Study Period: First Patient First Visit: 24-Aug-2009 Last Patient Last Visit: 05-Aug-2010 Early Termination Date of Study: 24-Jun-2010	**Development Phase:** 3	
Objectives: The objective of this study was to evaluate the safety and efficacy of dutogliptin in patients with type 2 diabetes mellitus (T2DM) who are receiving background therapy with pioglitazone.		
Study Design: This was a randomized, double-blind, placebo-controlled, multicenter, parallel-group study with a screening period of up to 12-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 pioglitazone 30 mg to 45 mg once daily 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 (DUT-MD-403) is summarized in a separate report.		
Diagnosis and Main Criteria for Inclusion: Adult male and female outpatients, 18-85 years of age, inclusive (except for Germany where the age criterion was 18-75 years, and India where the age criterion was 18-65 years, as per respective local country guidelines), who had been diagnosed with T2DM at least 3 months before the Screening Visit (Visit 1), with a body mass index of 20 to 48 kg/m^2, inclusive; a glycosylated hemoglobin (HbA_{1c}) level of 7.0% to10.0%, inclusive; and a fasting plasma C-peptide > 0.26 nmol/L (or > 0.8 ng/mL) at the Screening Visit (Visit 1) were eligible for enrollment. Patients may have been drug-treatment naive, or treated with a stable dose (minimum of 12 weeks) of pioglitazone (or rosiglitazone), or treated with a stable dose (minimum of 6 weeks) of any other oral hypoglycemic agent (OHA) as monotherapy at Visit 1. At randomization (Visit 4), patients had to have an HbA_{1c} level ≥ 7.0% and ≤ 10%, and an FPG level ≤ 270 mg/dL (15 mmol/L), values obtained at Visit 3. Patients with type I diabetes mellitus were not eligible for the study.		

Number of Patients:			
	Placebo	**Dutogliptin 400 mg**	**Total**
Total number of patients screened = 1605			
Randomized, N[a]	**123**	**128**	**251**
Safety, N	**123**	**127**	**250**

The Screened Population consisted of all patients who underwent the screening visit and were assigned a patient identification number.

The Randomized Population consisted of all patients in the Screened Population who were randomized to a treatment group.

The Safety Population consisted of all patients in the Randomized Population who took at least 1 dose of double-blind treatment.

a The planned number of patients to be randomized was approximately 400 patients. The target number of randomized patients (N=400) was not reached because the study was terminated early by the sponsor for business reasons.

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

Reference Therapy, Dose and Mode of Administration, Batch Number:
Matching Placebo tablets, one tablet/day, oral administration,

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 not performed in the study 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 FPG from baseline at Week 26/Visit 8 (LOCF)
- Percentage of patients reaching treatment goal of $HbA_{1c} < 7.0\%$ at Week 26/Visit 8 (LOCF)

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 (PK) and pharmacodynamic (PD) analyses listed below were planned for all patients in the study:

- Plasma dutogliptin levels before dosing and between 0.5 to 2 hours and 6 to 8 hours after drug dosing at baseline (Visit 4) and at Week 10/Visit 6, and before dosing and between 4 to 6 hours after dosing at Week 26/Visit 8.
- Percent ex vivo DPP4 inhibition before dosing and between 0.5 to 2 hours and 6 to 8 hours after drug dosing at baseline (Visit 4) and at Week 10/Visit 6, and before dosing and between 4 to 6 hours after dosing at Week 26/Visit 8.

Statistical Methods:

Efficacy: As planned, 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 postbaseline assessment of HbA_{1c}. The primary efficacy parameter was the change from baseline in HbA_{1c} at Visit 8 (LOCF). Between–treatment group differences for this parameter would be analyzed using an analysis-of-covariance (ANCOVA) model with treatment group and country as factors and baseline HbA_{1c} as a covariate.

Efficacy analyses were not performed because the study was terminated early by the sponsor for business reasons.

Safety: All the safety parameters, which were summarized descriptively on the basis of the Safety Population, were AEs, clinical laboratory parameters, vital sign measurements, and ECG parameters. For each parameter, the last assessment made before the first dose of DB investigational product (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: The target number of randomized patients (N=400) was not reached because the study was terminated early by the sponsor for business reasons. Of the 251 patients in the Randomized Population, 23 (9.2%) patients completed the study. "Study terminated by Sponsor" (82.1% of patients) was the most common reason for study discontinuation.

Demographics and Other Baseline Characteristics: The mean age of patients in the Safety Population was approximately 53 years. Most patients were male (52%), Non-Hispanic (81.6%), and Caucasian (66%). The mean body mass index of all patients in the Safety Population was 32.26 kg/m2.

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

Pharmacokinetic Results: Plasma dutogliptin concentrations were measured in 1 patient (Patient 604304007) who exhibited abnormal results from liver functions tests (LFTs) performed during the study. The plasma concentration data are included in the narrative for this patient. Available PK data are presented in Listing 16.8.2

Safety Results:

- No deaths were reported in the study.
- Treatment-emergent serious adverse events (SAEs) were reported in 7 patients (4 [3.3%] patients in the placebo group and 3 [2.4%] 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 8 patients (3 [2.4%] patients in the placebo group and 5 [3.9%] patients in the dutogliptin group). One event, chest pain, reported in the placebo group was considered serious.

Overall, TEAEs were reported in 51 (41.5%) patients in the placebo group and 52 (40.9%) patients in the dutogliptin group. TEAEs reported in at least 2% of patients in the dutogliptin group were edema (6 [4.7%] patients), peripheral edema (5 [3.9%] patients), and urinary tract infection (3 [2.4%] patients). These 3 TEAEs were reported in similar frequencies in the placebo group: edema, 6 (4.9%) patients; peripheral edema, 7 (5.7%) patients; and urinary tract infection, 1 (0.8%) patient.

CONCLUSIONS:

Study DUT-MD-304 was a Phase 3, randomized, DB, placebo-controlled, multicenter study to evaluate the safety and efficacy of dutogliptin in adult patients with T2DM who were receiving background treatment with pioglitazone.

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 dutogliptin and placebo groups. A similar percentage of patients in each treatment group reported TEAEs (41.5% placebo; 40.9% dutogliptin). There were a small number of SAEs, similar in incidence in both treatment groups (placebo 2.4% and dutogliptin 3.3%). 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 chest pain (reported in 1 patient in each treatment group). The rate of patients who discontinued after randomization due to AEs was similar in both groups (3 [2.4%] in the placebo group and 5 [3.9%] in the dutogliptin group).

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