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-303		
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 Glimepiride With or Without Metformin		
Investigators: Multi-center study; a complete list of Investigators is provided in Appendix 16.1.4 of the clinical study report		
Study Centers: 171 study centers (5 in Belarus, 1 in Colombia, 7 in Hungary, 18 in India, 5 in Lithuania, 10 in Peru, 10 in Romania, 115 in the US)		
Publication (reference): Not applicable.		
Study Period (years): First Patient First Visit: 22-Jul-2009 Last Patient Last Visit: 29-Jul-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 were receiving background therapy with glimepiride with or without metformin.		
Study Design: This was a randomized, double-blind, placebo-controlled, multicenter, parallel-group study with a screening period of up to 10 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 double-blind treatment period. Randomization was stratified by whether or not patients were receiving background metformin therapy. Patients received background treatment with glimepiride alone or in combination 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 (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 India where the age criterion was 18-65 years as per local country guideline), 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% 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 (Visit 1) were eligible for enrollment. Patients may have been drug-treatment naïve (allowed after Amendment #2 of the protocol) or either on a stable dose of glimepiride with or without metformin before entering the study or willing to be switched during the screening period from their previous sulfonylurea medication to treatment with glimepiride with or without metformin. 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 1 diabetes mellitus were not eligible for the study.

Number of Patients:

	Placebo			***Dutogliptin 400 mg***			***Total***		
	Glimepiride	*Glimepiride + Metformin*	*Total Placebo*	*Glimepiride*	*Glimepiride + Metformin*	*Total Dutogliptin*	*Total Glimepiride*	*Total Glimepiride + Metformin*	*Total All Patients*
Total number of patients screened = 2118									
Randomized, N[a]	124	220	344	125	206	331	249	426	675
Safety, N	122	216	338	125	203	328	247	419	666

The Screened Population consisted of all patients who underwent the Screening Visit (Visit 1) and received a patient identification number.

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

The Safety Population consisted of all randomized patients who receive at least one dose of investigational product.

a The planned number of patients to be randomized was approximately 325 patients allocated to each of the 2 background therapy subpopulations, glimepiride-only and glimepiride with metformin. The target number of randomized patients of approximately 325 in the glimepiride-only subpopulation 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, 1 tablet/day, oral administration, [redacted]

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

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

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 from baseline in HbA_{1c} at Visit 8/ Week 26 (Last observation carried forward [LOCF])

Secondary:
• Change from baseline in FPG at Visit 8/Week 26 (LOCF)
• Percentage of patients reaching the treatment goal of HbA1c < 7% at Visit 8 (LOCF)

Safety:
Adverse event (AE) recording**,** clinical laboratory measures **,** vital signs parameters (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 one postbaseline assessment of HbA_{1c}.The primary efficacy parameter was the change from baseline in HbA_{1c} at Visit 8 (last observation carried forward [LOCF]). Between–treatment group differences for this parameter would be analyzed using an analysis-of-covariance (ANCOVA) model with treatment group, background therapy with oral hypoglycemic agents (OHA) (glimepiride alone vs glimepiride plus metformin), 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 double-blind 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: Of the 675 patients randomized, 174 (25.8%) completed the study, and 501 (74.2%) were prematurely discontinued. The most common reasons for premature discontinuation were: study terminated by sponsor (420 [62.2%] patients); lost to follow-up (27 [4.0%] patients); withdrawal of consent (17 [2.5%] patients); and adverse event (13 [1.9%] patients).

Demographics and Other Baseline Characteristics: The mean age of patients in the safety population was approximately 55 years. Most patients were male (56.3%), Non-Hispanic/Non-Latino (76.9%), and Caucasian (70.6%). The mean body mass index of in the safety population was 31.64 kg/m^2.

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

Pharmacokinetic Results: Plasma dutogliptin concentrations were measured for 2 patients (Patients 112303020 and 056303007) who exhibited abnormal results from liver function tests (LFTs) performed during the study. The plasma concentration data are included in the narratives for these patients. Available PK data are presented in Listing 16.8.2.

Safety Results:

- No deaths were reported during the DB treatment period. One patient, a 53-year-old male, died of a cardiac arrest during the screening period.
- Treatment-emergent SAEs were reported in 14 patients: 6 (1.8%) patients in the placebo group and 8 (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 after at least one dose of double-blind IP were reported in 13 patients: 8 (2.4%) patients in the placebo group and 5 (1.5%) patients in the dutogliptin group. Hemorrhagic stroke, reported in 1 patient in the placebo group was the only treatment-emergent SAE that led to discontinuation.
- Overall, TEAEs were reported in 129 (38.2%) patients in the placebo group and 120 (36.6%) patients in the dutogliptin group. TEAEs reported in at least 2% of patients in the dutogliptin group were hypoglycemia (29 [8.8%] patients) and peripheral edema (7 [2.1%] patients). These TEAEs were reported in the placebo group as follows: hypoglycemia, 18 (5.3%) patients and peripheral edema 7 (2.1%) patients.

CONCLUSIONS:

Study DUT-MD-303 was a randomized, double-blind, placebo-controlled, multicenter study to evaluate the safety and efficacy of dutogliptin in adult patients with type 2 diabetes mellitus on background treatment with glimepiride with or without metformin.

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 data 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 (38.2% [129 patients] in the placebo group; 36.6% [120 patients] in the dutogliptin group). There were a small number of SAEs, similar in number in both treatment groups (placebo 6 [1.8%] and dutogliptin 8 [2.4%]). None of the SAEs were considered to be related to the IP. Hemorrhagic stroke, reported in 1 patient in the placebo group, was the only treatment-emergent SAE that led to discontinuation. The rate of patients who received at least one dose of double-blind IP and who discontinued due to AEs was similar in both groups (8 [2.4%] in the placebo group and 5 [1.5%] in the dutogliptin group).

Date of the Report: 09-Feb-2011