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-403

Title of Study: A Phase III, Multicenter, Double-blind, Active-Controlled, 52-Week Extension Study to Evaluate the Safety and Efficacy of Dutogliptin in Patients With Type 2 Diabetes Mellitus Receiving Background Treatment With Glimepiride Alone or in Combination With Metformin or with Pioglitazone Alone

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

Study Center(s): 49 study centers in the United States

Publication (reference): Not applicable.

Study Period:. First Patient First Visit: 10 Mar 2010 Last Patient Last Visit: 02 Aug 2010 Early Termination Date of Study: 23 Jun 2010	**Development Phase:** 3

Objectives: The primary objective of this extension study was to demonstrate the long-term safety of dutogliptin in patients with Type 2 Diabetes Mellitus (T2DM). The secondary objective of this extension study was to demonstrate the long-term efficacy of dutogliptin in patients with T2DM.

Study Design:
This was a multicenter, double-blind, active-controlled, double-dummy, parallel-group, fixed-dose, 52-week extension study for T2DM patients who successfully completed either core study DUT-MD-303 or DUT-MD-304. Patients who were randomized to dutogliptin 400 mg in the core study continued this treatment and concomitantly received sitagliptin-matched placebo. Patients who were randomized to placebo in the core study received active control (encapsulated sitagliptin 100 mg) and dutogliptin-matched placebo. Based on their core study background treatment regimen, patients received background therapy with glimepiride alone or in combination with metformin (DUT-MD-303) or with pioglitazone alone (DUT-MD-304), as appropriate.

Diagnosis and Main Criteria for Inclusion:
Adult male and female outpatients who successfully completed either core study DUT-MD-303 or DUT-MD-304 and who were currently receiving treatment for T2DM as set forth in either core study DUT-MD-303 or DUT-MD-304.

Number of Patients:

	Sitagliptin 100 mg	***Dutogliptin 400 mg***	***Total***
Enrolled, N[a]	**74**	**67**	**141**
Safety, N	**73**	**66**	**139**

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

Safety Population consisted of all patients in the Enrolled Population who took at least 1 dose of investigational product (IP) in the extension study.

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

Reference Therapy, Dose and Mode of Administration, Batch Number:
Encapsulated sitagliptin tablets, 100 mg/day (as a capsule containing two 50-mg tablets), oral administration,
Placebo tablets, oral administration,
Placebo capsules, oral administration,

Duration of Treatment: 52 weeks

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.
Change from baseline in HbA1c and change from baseline in fasting plasma glucose at each visit (post–Visit 1).

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.

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 who had at least 1 post–Visit 1 assessment of HbA1c or FPG. The baseline to be used in the statistical analyses was the baseline (Visit 4) from the core study. The efficacy parameters were change from baseline in hemoglobin A_{1c} and fasting plasma glucose at each visit (post-Visit 1). Efficacy parameters would have been summarized by treatment group descriptively.

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

Safety: Safety parameters, which were summarized descriptively on the basis of the Safety Population, were AEs; clinical laboratory, vital sign, and ECG parameters; and targeted physical examination findings. For each safety parameter, the last assessment made before the first dose of double-blind IP in core study DUT-MD-303 or core study DUT-MD-304 will be used as the baseline for all analyses of that parameter.

SUMMARY OF RESULTS:

Disposition: The study was terminated early by the sponsor for business reasons. Of the 139 patients who took at least 1 dose of IP in the extension study, no patients completed the study; "Study terminated by Sponsor" [130 (93.5%) patients] was the most common reason for study discontinuation.

Demographics and Other Baseline Characteristics: The mean age of patients was 55 years, range 30 to 84 years. The majority of patients were male (58.3%), Caucasian (81.3%), and non-Hispanic (71.2%).

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

Safety Results:
- One newly-emergent SAE (cerebrovascular accident) was reported in one patient (1.5%) in the dutogliptin treatment group. It was considered by the investigator to be not related to the IP.
- There were no deaths or discontinuations due to AEs in this study.
- Overall, TEAEs were reported in 14 (19.2%) patients in the sitagliptin group and 17 (25.8%) patients in the dutogliptin group during the active-controlled extension study. The incidence and types of NEAEs reported were similar: 13 (17.8%) patients in the sitagliptin group and 17 (25.8%) patients in the dutogliptin group. These data suggest that no unanticipated types of AEs appeared after continued exposure to dutogliptin.
- The most common TEAEs were hypoglycemia, nausea, and pain in extremity, each at an incidence of 2 (3.0%) patients in the dutogliptin group. Only hypoglycemia and nausea were newly-emergent, each reported in 2 (3.0%) patients in the dutogliptin group. Hypoglycemia was reported at a similar incidence (2 [2.7%] patients) in the sitagliptin group; nausea was not reported in the sitagliptin group.

CONCLUSIONS:

Study DUT-MD-403 was a Phase 3, multicenter, double-blind, active-controlled, double-dummy, parallel-group, fixed-dose, 52-week extension study designed to enroll patients with T2DM who successfully completed either core study DUT-MD-303 or DUT-MD-304.

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

Safety data showed that treatment with dutogliptin was generally tolerated well in adult patients with T2DM who were receiving treatment with glimepiride alone or in combination with metformin, or with pioglitazone alone. A comparable number of patients in each treatment group (14 [19.2%] sitagliptin, 17 [25.8%] dutogliptin) reported TEAEs during the active-controlled extension study. The incidence and types of NEAEs reported were similar: 13 (17.8%) patients in the sitagliptin group and 17 (25.8%) patients in the dutogliptin group. These data suggest that no unanticipated types of AEs appeared after continued exposure to dutogliptin. One newly-emergent SAE of cerebrovascular accident was reported in a patient in the dutogliptin group; it was not considered to be related to the IP. No patients in either treatment group discontinued due to AEs.

Date of the Interim Report: [Date final report was sent for signature (must match title page)]