PFIZER INC.

These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert.
For publications based on this study, see associated bibliography.

PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: PF-00915275

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: Diabetes Mellitus; not approved for marketing.

NCT NO.: NCT00427401

PROTOCOL NO.: A8441003

PROTOCOL TITLE: A Double Blind, Placebo Controlled, Parallel Group Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of PF-00915275 after Oral Administration to Subjects with Type 2 Diabetes Mellitus for 4-Weeks

Study Center(s): 1 study center in Belgium

Study Initiation and Completion Dates: 06 Feb 2007 to 15 June 2007
This study was terminated prematurely.

Phase of Development: Phase 2a

Study Objective(s):

Primary Objective:

To evaluate the effects of an oral dose of PF-00915275 (10 mg) on 24-hour mean daily glucose levels when administered as tablets for 4 weeks in subjects with type 2 diabetes mellitus (T2DM).

Secondary Objectives:

- To evaluate the safety and tolerability of PF-00915275 (10 mg) when administered as tablets to subjects with T2DM for 4 weeks.
- To characterize the pharmacokinetics of PF-00915275 following administration of PF-00915275 (10 mg) as tablets to subjects with T2DM for 4 weeks.
- To evaluate the pharmacodynamic effect of an oral dose of PF-00915275 (10 mg) on 11β hydroxysteroid dehydrogenase type 1 (11βHSD1) inhibition when administered as tablets for 4 weeks in subjects with T2DM.

METHODS

Study Design: This study was originally designed as a randomized, placebo-controlled, double-blind, multiple-dose study. Following the initial screening visit and prior to planned randomization, each subject underwent an additional selection based on a PK screen. The PK screen entailed the unblinded administration of a single dose of 10 mg PF-00915275 as tablets and collection of PK specimens over the first 36 hours following dose administration. Population modeling and simulation of the screening PK profiles were used to predict the steady state area under the concentration-time curve (AUC) to determine whether an individual subject was expected to exceed the no observed adverse effect level (NOAEL) AUC (12.6 µg.hr/ml). If a subject was predicted to exceed the NOAEL limits (AUC and Cmax) (s) he/she was to be excluded from entering in the study. Subjects were to be randomized to receive 10 mg of PF-00915275 or placebo (20 subjects per arm) in a double-blind manner once daily for 4 weeks. However, this study (A8441003) was terminated prematurely following the PK screening dose in 7 subjects, and no subjects were randomized.

Number of Subjects (Planned and Analyzed): Up to 60 T2DM subjects were planned for inclusion in the PK screen, and 40 subjects were planned for enrollment into the study. A total of 7 subjects were administered the PK screening dose of PF-00915275 10 mg. No subject was enrolled in the planned, double blind, randomized portion of the study.

Diagnosis and Main Criteria for Inclusion: The study population included male subjects and female subjects of nonchildbearing potential with T2DM, who were between 18 and 75 years of age, with a body mass index (BMI) of ≥25 to ≤40 kg/m^2, a weight of ≥50 kg (110 lbs), an Hb A1c of ≥7.5%, and had fasting blood glucose levels in the range of 140 to 240 mg/dL.

Study Treatment: All subjects received a single, open-label dose of PF 00915275 10 mg (administered as five 2-mg tablets) as part of the PK screen. Following the PK screen, subjects enrolled in the study were to receive either PF 00915275 10 mg (five 2 mg tablets) or placebo (5 PF 00915275-matched placebo tables) once daily for 4 weeks. All subjects were also to receive prednisone 10 mg on Days 0 and 14.

Efficacy Evaluations: The ability of PF-00915275 to lower glucose levels was to be evaluated using the following methods: 24-hour mean glucose levels; fasting blood glucose levels; GlycoMark™ measurement; and Hb A1c measurement. However, no efficacy evaluations were performed.

Pharmacokinetic Evaluations: Plasma samples for the PK screening analyses of PF-00915275 were to be collected predose (within 15 minutes of dosing) at 0 hour and up to 36 hours postdose. Pharmacokinetic samples were analyzed using a validated analytical method in compliance with Pfizer standard operating procedures. Because the development of PF-00915275 was terminated, no PK parameters were calculated.

Pharmacodynamic Evaluations: For prednisone/prednisolone, plasma samples were to be collected on Days 0 and 14 pre-prednisone dose and at 20, 40, 60, 80, and 100 minutes and 2,

2.5, 3, 3.5, 4, 5, and 6 hours post-prednisone dose using tubes containing heparin as the anticoagulant. The following prednisone and prednisolone PK endpoints were planned for evaluation of the PD effects of PF-00915275: AUC from time 0 to 6 hours (AUC_{0-6}), Cmax, and Tmax. Urine samples were to be collected and pooled over the 24-hour interval during Day -1 and from 0-24 hours postdose on Day 28 for PD analysis. Because the development of PF-00915275 was terminated, no PD parameters were calculated.

Safety Evaluations: Safety evaluations included clinical monitoring, vital signs (blood pressure and pulse rate), 12-lead electrocardiograms, adverse events (AEs), and safety laboratory tests.

Statistical Methods: Statistical analyses were not performed.

RESULTS

Subject Disposition and Demography: A total of 7 subjects were administered the PK screening dose of PF-00915275 10 mg. No subject was enrolled in the planned, double-blind, randomized portion of the study. All subjects who were administered the PK screening dose of study drug were included in the PK, safety, and laboratory analyses. Six male subjects and 1 female subject were enrolled in the screening portion of the study. The age range of the male subjects was 43 to 53 years old and the female subject was 72 years old. One male subject was black and the remaining subjects were white. The weight range of the subjects was 89 to 109 kg and the BMI range was 27.7 to 36.7 kg/m^2. All 7 subjects were taking metformin for T2DM.

Efficacy Results: Due to premature termination of this study, no efficacy evaluations were performed.

Pharmacokinetic Results: Seven subjects were screened and dosed orally with 10 mg PF-00915275. The plasma concentration of PF-00915275 increased and reached peak at around 10 hours after dosing, and only declined very slowly afterwards. At 36 hours postdose, the concentration of study drug in all subjects was only slightly lower than it was at the maximum, which occurred at approximately 10 hours postdose, suggesting a long apparent terminal half life. However, in previous studies (A8441001 and A8441002), when PF-00915275 was given as oral solution, its terminal half life ranged only from 26 to 37 hours. The long apparent terminal half life observed in this study was much longer than 37 hours. It was not clear what caused the long apparent terminal half life. It was unlikely that the elimination of PF-00915275 would have differed significantly between these two studies. More likely, the terminal phase observed in these subjects represented the slow dissolution/absorption process of the current tablet formulation. Consistently, a qualitative estimation of the median Tmax was approximately 10 hours, which was longer than what was observed in previous studies (1-2 hours). This was also likely due to slow dissolution/absorption process of the current tablet formulation.

Safety Results: There were no deaths and no serious adverse events (SAEs) during this study. As this study was terminated following a single dose of PF-00915275, no subject was discontinued due to an AE. Adverse events were experienced by 2 subjects. The only

treatment-emergent AE was mild erectile dysfunction that was experienced by 1 subject. The erectile dysfunction was considered to be related to diabetes and not related to study drug. The same subject also experienced mild conjunctivitis that was related to a viral infection and not related to the study drug. Another subject experienced 2 occurrences of a mild furuncle that were related to bacterial infection and not related to study drug.

Two subjects had fasting glucose levels of protocol-specified potential clinical concern during the study. However, no subjects had changes in safety laboratory findings, ECGs, and vital signs that were considered to be clinically significant.

CONCLUSION(S):

- The plasma concentration of PF-00915275 increased and reached peak at around 10 hours after dosing, and only declined very slowly afterwards. At 36 hours postdose, the concentration of study drug in all subjects was only slightly lower than it was at the 10 hours postdose time point, indicating a long terminal half-life. Future development of PF-00915275 was discontinued due to a low confidence in achieving the product target profile.

- There were no deaths, no serious adverse events, and no treatment-related adverse events following a single dose of PF-00915275.