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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: PF-00734200

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS:

NATIONAL CLINICAL TRIAL NO.: NCT00473525

PROTOCOL NO.: A7941005

PROTOCOL TITLE: A Phase 2a, Randomized, Placebo Controlled, Parallel Group, Multiple Dose Study to Evaluate the Efficacy, Safety and Tolerability of 12-Week Oral Administration of PF-00734200 Tablets to Subjects with Type 2 Diabetes Mellitus on Stable Treatment with Metformin

Study Centers: Subjects were enrolled at 75 centers: 4 centers in Columbia, 4 centers in Germany, 1 center in Italy, 4 centers in Spain, 3 centers in Sweden, and 59 centers in the United States. Subjects were treated at 70 of these 75 of these centers (no subjects were treated at 1 center in Columbia and 4 centers in the United States).

Study Initiation and Completion Dates: 03 July 2007 to 26 June 2008

Phase of Development: Phase 2

Study Objectives: The primary objective of this study was to compare the effect of multiple oral doses of PF-00734200 tablet versus placebo on change from baseline to 12 weeks of glycosylated hemoglobin (HbA1c) levels and evaluate dose response in subjects with type 2 diabetes mellitus (T2DM) on a stable dose of metformin hydrochloride (metformin). The term 'stable dose of metformin' was defined as the same dose of metformin for at least 2 months prior to randomization.

The secondary objectives of this study were:

1. To evaluate the effect of multiple oral doses of PF-00734200 tablet on change from baseline to 12 weeks of insulin area under the curve (AUC) following mixed-meal tolerance test (MMTT) in subjects with T2DM.

2. To evaluate the proportion of subjects achieving the current American Diabetic Association (ADA) glycemic goal of HbA1c <7%.

3. To evaluate the safety and tolerability of multiple oral doses of PF-00734200 tablet administered to subjects with T2DM.

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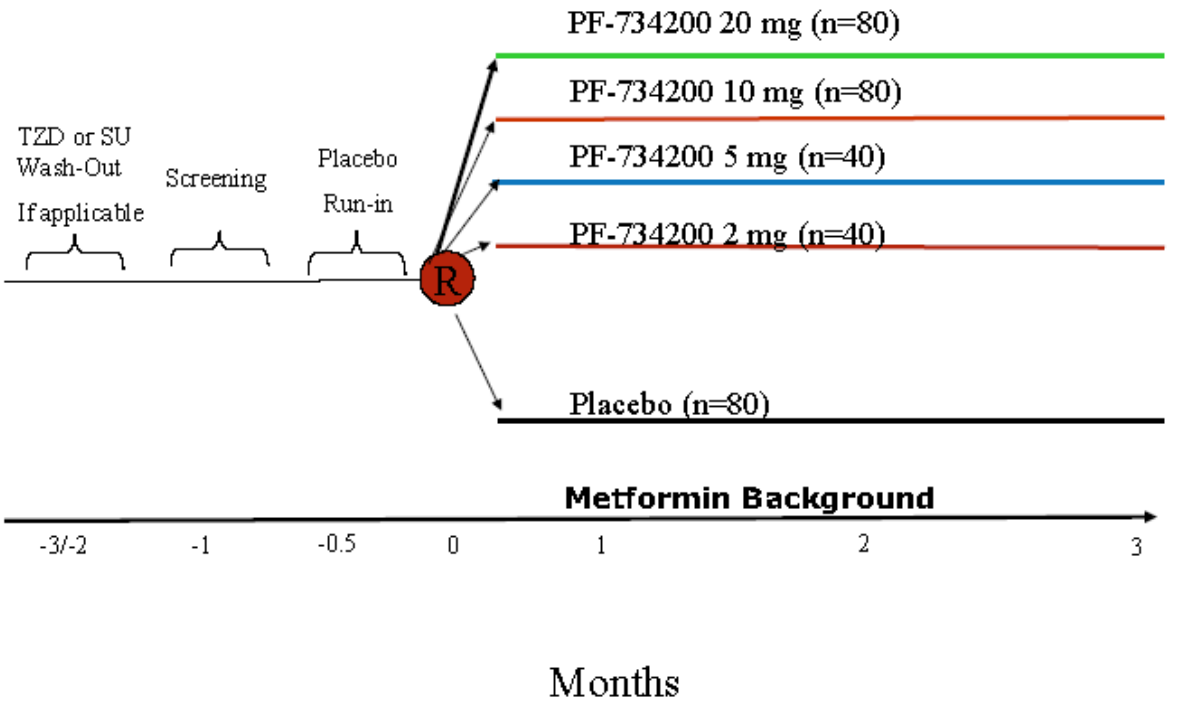
METHODS

Study Design: This was a randomized, double blind, placebo controlled, multiple dose, 5-arm, parallel-group study (see Figure S1).

Figure S1. Study Design Schematic



Abbreviations: SU=sulfonylurea; TZD= thiazoladinedione

The Screening period occurred within 28 days of the first double-blind dose. Subjects meeting the entry criteria were provided with dietary advice based on current ADA recommendations by a nutritionist, dietician, or equally-qualified individual and participated in a placebo run-in period, that started on Day 14 (ie, before the first double-blind dose) to allow them to adjust to the suggested nutritional and caloric guidelines and study drug tablet self administration.

The study was designed to include subjects receiving several different regimens of treatment for their T2DM:

- metformin monotherapy
- metformin + sulfonylurea
- metformin + TZD (pioglitazone or rosiglitazone)

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Subjects receiving metformin monotherapy proceeded immediately to the Screening Visit and completed the study procedures. Subjects who were receiving metformin + sulfonylurea or metformin + TZD were eligible to be screened for this study if the Investigator thought that they would meet the HbA1c and fasting plasma glucose criteria following the washout of either the sulfonylurea (4 weeks) or TZD (8 weeks).

Number of Subjects (Planned and Analyzed): Approximately 640 subjects with T2DM, and on a stable dose of metformin, were planned to be screened to achieve 320 subjects enrolled at 35 to 40 sites worldwide. The actual number of subjects screened was 766 of whom 302 subjects were assigned to study treatment and 301 subjects were treated.

Diagnosis and Main Criteria for Inclusion: The study population included males and females (of nonchildbearing potential) with T2DM; subjects were to be 18 to 70 years of age, inclusive, have a Body Mass Index (BMI) of ≥25.0 to ≤45.0 kg/m^2, weigh ≥50 kg (110 lb), and have an HbA1c >7-11%.

Study Treatment: All daily doses were administered orally under fasting conditions.

Placebo Run-In Period: Starting on Day -14 subjects received single-blind daily treatment of placebo.

Double-Blind Treatment Period: On Day 1 subjects were randomly assigned to receive 1 of the following 5 daily treatments for 12 weeks:

- PF-00734200 2 mg (n=40)
- PF-00734200 5 mg (n=40)
- PF-00734200 10 mg (n=80)
- PF-00734200 20 mg (n=80)
- Matching Placebo (n=80)

Efficacy Evaluations: The primary objective of this study was to compare the effect of multiple oral doses of PF-00734200 tablet versus placebo on change from baseline to 12 weeks of HbA1c levels and evaluate dose response in subjects with T2DM on a stable dose of metformin. The primary analysis population for all efficacy analysis includes all subjects who completed the 12 weeks of study treatment (Per Protocol Set).

The secondary efficacy variables assessed in this study were:

- Fasting plasma glucose (FPG) representing glucose concentration at 0 minutes, G_0
- AUC(0-180) of glucose following MMTT
- AUC(0-180) of insulin following MMTT
- Change in glucose concentration from 0 to 30 minutes (ΔC30) following a MMTT
- Change in insulin concentration from 0 to 30 minutes (ΔC30) following a MMTT
- Ratio of insulin AUC / glucose AUC
- Ratio of insulin ΔC30 / glucose ΔC30

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The exploratory variables assessed in this study were:

- GlycoMark
- Body weight
- 2-hour post-prandial glucose (glucose reading corresponding to 120 minutes following MMTT = G120)
- Change in glucose concentration from 0 to 120 minutes (ΔC120) following a MMTT
- Change in glucose concentration from 0 to 180 minutes (ΔC180) following a MMTT
- HOMA-B (measure of pancreatic B-cell function)

Pharmacokinetic Evaluations: Blood samples for pharmacokinetic assessment of PF-00743200 were collected fasting before dosing on Days 14, 56 and 84 (or premature discontinuation) and at 0.75, 1.75, and 3.25 hours postdose on Day 84 for all randomized subjects.

Safety Evaluations: Safety and tolerability were assessed by physical examinations, adverse event (AE) monitoring, clinical safety laboratory tests, vital sign measurements, and 12-lead electrocardiograms (ECGs).

Statistical Methods:
Efficacy: The primary analysis consisted of analysis of change from baseline to Week 12 in HbA1c using the analysis of covariance (ANCOVA) model with baseline as a covariate and the E_{max} (maximum effect attributable to the drug) model using the Per Protocol Set. Analysis using the Full Analysis Set (LOCF) was performed as secondary analysis. Secondary and exploratory endpoints of changes from baseline in HbA1c, FPG, 2-hour postprandial glucose, glucose ΔC_{30}, insulin ΔC_{30}, Ratio of insulin ΔC_{30} / glucose ΔC_{30}, GlycoMark, glucose ΔC_{120}, glucose ΔC_{180}, HOMA-B, and body weight were analyzed using ANCOVA model adjusting for baseline values at Weeks 2, 4 and 8 for HbA1c, Weeks 2, 4, 8, and 12 for FPG, and GlycoMark; Week 12 for all other endpoints. An analysis of responders (subject with postbaseline HbA1c <7%) was performed at Weeks 2, 4, 8, and 12 using the logistic regression model adjusting for baseline values. Rank-based regression of change from baseline in AUC(0-180) for glucose and insulin following MMTT and the ratio of AUC for insulin over AUC for glucose ($AUC_{insulin}$ / $AUC_{glucose}$) was done at Week 12. Dose response analysis of change from baseline in FPG and 2-hour postprandial glucose was done at Week 12. Per Protocol Set was used for the analysis of all secondary and exploratory endpoints.

Pharmacokinetics: All concentrations of PF-00734200 were summarized by dose and nominal time postdose regardless of actual time, where the set of statistics included n, mean, median, standard deviation, coefficient of variation and the number of concentrations above the lower limit of quantification were provided.

Safety: Safety data were presented in tabular and/or graphical format and summarized descriptively.

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RESULTS

Subject Disposition and Demography: Subjects were treated at 70 centers in Colombia, Germany, Italy, Spain, Sweden, and the United States. Of the 766 subjects screened, 302 subjects were assigned to study treatment and 301 subjects were treated (Table S1). One subject was assigned to treatment in the PF-00734200 2-mg group but was not treated due to an AE of cardiac anterolateral ischemia. A total of 278 subjects completed the study. Most discontinuations were not related to study drug.

All treatment groups were similar at baseline with respect to demographic characteristics such as age, gender, and BMI. Comparable HbA1c results were also noted across the treatment groups. The majority of subjects were males (66%); 61% of subjects were white. The mean age ranged from 55.7 years in the 10-mg group to 57.2 years in the placebo group; the overall ages ranged from 30 to 71 years.

All subjects in this study had a primary diagnosis of T2DM. The duration since first diagnosis ranged from a mean of 6.5 years in the 20-mg group to 9.4 years in the 2-mg group.

Table S1. Subject Disposition and Data Sets Analyzed

Number (%) of Subjects	Placebo	PF-00734200 2 mg	PF-00734200 5 mg	PF-00734200 10 mg	PF-00734200 20 mg
Assigned to Study Treatment	76	38	38	77	73
Treated	76	37	38	77	73
Completed	70 (92.1)	34 (89.5)[a]	34 (89.5)	71 (92.2)	69 (94.5)
Discontinued	6 (7.9)	3 (7.9) [a]	4 (10.5)	6 (7.8)	4 (5.5)
Analyzed for Efficacy					
Full Analysis Set	74 (97.4)	37 (97.4)	37 (97.4)	77 (100)	72 (98.6)
Per Protocol Set	72 (94.7)	37 (97.4)	37 (97.4)	76 (98.7)	72 (98.6)
Analyzed for Safety					
Adverse events	75 (98.7)	37 (97.4)	38 (100)	77 (100)	73 (100)
Laboratory data	76 (100)	37 (97.4)	37 (97.4)	77 (100)	73 (100)

a. Percent calculated based on number of subjects assigned to study treatment (N=38); however, only 37 subjects were actually treated.

Efficacy Results:

- Results from the analysis of covariance of change from baseline showed that PF-00734200 was statistically significantly superior to placebo in reducing HbA1c from baseline to Week 12 at doses of 5 to 20 mg/day.

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- Results from an E_{max} model analysis of HbA1c change from baseline at Week 12 (using a fixed slope of 3) estimated a maximal response of -0.75% (-1.02, -0.48) over placebo response.

- A higher proportion of subjects meeting ADA HbA1c goals (defined as HbA1c <7%) were noted for all treatment groups ≥5 mg PF-00734200 versus placebo at Weeks 8 and 12. The odds of responses in these treatment groups were statistically significantly higher (p-value ≤0.05) compared to the odds of response in the placebo group.

- There was a high level of variability in fasting plasma glucose results. However, despite this variability there was a trend towards reduction in fasting plasma glucose levels after treatment with PF-00734200. Results from an E_{max} model analysis of fasting plasma glucose change from baseline at Week 12 (using a fixed slope of 3) showed significant response at 10 mg and 20 mg doses over placebo response.

- A statistically significant reduction from baseline in glucose AUC values was noted at Week 12 for the 20 mg PF-00734200 group versus placebo (p=0.0027).

- Results of 2-hour postprandial glucose showed that subjects in the 20-mg group had the greatest reduction in glucose levels at Week 12.

- The median percent change from baseline for the ratio of the insulin AUC (0 to 180 minutes) over glucose AUC (0 to 180 minutes) following MMTT was statistically significantly higher (p-value ≤0.05) for the ≥10 mg/day PF-00734200 groups compared with the placebo group.

Pharmacokinetic Results: Mean concentrations increased approximately proportionally with dose. Mean trough concentrations are comparable on 3 separate visits indicating that steady state had been reached by Day 14.

Safety Results: There were no deaths during this study. Three subjects (Table S2) each reported 1 serious adverse event (SAE); these SAEs included deep vein thrombosis (10-mg group), myocardial infarction (10-mg group; led to discontinuation from the study), and hypertensive crisis (placebo group).

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Table S2. Nonfatal Serious Adverse Events

Subject Number	Age/ Sex	MedDRA (v11.0) Preferred Term	Start/Stop Day[a]	Severity	Causality
Placebo					
10761023	57/F	Hypertensive crisis	12/13	Severe	Other (emotional crisis)
PF-00734200 10 mg					
10221060	65/M	Myocardial infarction[b]	22/24	Moderate	Other illness[c]
10651005	57/M	Deep vein thrombosis[d]	24/37	Severe	Disease under study

Abbreviations: F=female; M=male; MedDRA=medical Dictionary for Regulatory Activities; SAE=serious adverse event

a. Day relative to start of study treatment. First day of study treatment = Day 1
b. Subject permanently discontinued due to this SAE
c. History of hypertension/dyslipidemia
d. Study drug stopped temporarily due to this SAE

Five of the 301 subjects (1.7%) treated were discontinued from the study due to AEs (all occurred in PF-00734200 treated subjects; Table S3).

Table S3. Permanent Discontinuations Due to Adverse Events

Subject Number	Age/ Sex	MedDRA (v11.0) Preferred Term	Start/Stop Day[a]	Severity	Causality
PF-00734200 2 mg					
10601017	41/M	Blood creatinine increased	19/>30	Moderate	Other[b]
PF-00734200 5 mg					
10621003	63/F	Hyperglycemia	20/>35	Moderate	Study drug
PF-00734200 10 mg					
10221060	65/M	Myocardial infarction[c]	22/24	Moderate	Other illness[d]
10601007	61/M	Feeling jittery	57/>85	Mild	Study drug
PF-00734200 20 mg					
10261001	66/F	Urticaria	18/65	Moderate	Study drug

Abbreviations: F=female; M=male; MedDRA=Medical Dictionary for Regulatory Activities; SAE=serious adverse event

a. Day relative to start of study treatment. First day of study treatment = Day 1
b. Subject's primary care physician started new blood pressure medications (lisinopril and furosemide) approximately 12 days prior to start of the AE.
c. SAE
d. History of hypertension/dyslipidemia

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A total of 130 subjects (or 43%) reported at least 1 AE during this study (regardless of causality; Table S4). The most common AEs were upper respiratory tract infection, headache, and nasopharyngitis.

Table S4. Summary of Most Common (Reported in >2 Subjects Across the Treatment Groups) Adverse Events: All Causality

MedDRA (v11.0) Preferred Term	Placebo N=76	PF-00734200 2 mg N=37	PF-00734200 5 mg N=38	PF-00734200 10 mg N=77	PF-00734200 20 mg N=73
Number (%) with any AE	35 (46.1)	18 (48.6)	17 (44.7)	30 (39.0)	30 (41.1)
URTI	1 (1.3)	3 (8.1)	0	3 (3.9)	2 (2.7)
Headache	5 (6.6)	1 (2.7)	1 (2.6)	0	1 (1.4)
Nasopharyngitis	1 (1.3)	1 (2.7)	3 (7.9)	2 (2.6)	1 (1.4)
Pain in extremity	2 (2.6)	0	3 (7.9)	1 (1.3)	1 (1.4)
Diarrhea	3 (3.9)	0	0	1 (1.3)	2 (2.7)
Dizziness	1 (1.3)	0	0	2 (2.6)	2 (2.7)
Nausea	0	0	1 (2.6)	2 (2.6)	1 (1.4)
Urinary tract infection	1 (1.3)	0	0	1 (1.3)	2 (2.7)
Viral URTI	0	2 (5.4)	0	2 (2.6)	0
Fall	1 (1.3)	1 (2.7)	1 (2.6)	0	1 (1.4)
Peripheral edema	2 (2.6)	1 (2.7)	1 (2.6)	0	0
Hypertension[a]	1 (1.3)	1 (2.7)	0	1 (1.3)	2 (2.7)
Constipation	1 (1.3)	0	0	1 (1.3)	1 (1.4)
Gastroenteritis	0	1 (2.7)	1 (2.6)	1 (1.3)	0
Influenza	0	0	1 (2.6)	2 (2.6)	0
Tendonitis	1 (1.3)	1 (2.7)	0	1 (1.3)	0
Cough	0	0	1 (2.6)	2 (2.6)	0
Rash	0	0	1 (2.6)	0	2 (2.7)

Abbreviations: URTI = upper respiratory tract infection; AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities

[a] Does not include 1 subject with an SAE of hypertensive crisis.

Almost all AEs were mild or moderate in intensity; only 4 were severe. Treatment-related AEs were reported for 59 (20%) subjects with the most common being diarrhea and headache. Five of the 301 subjects treated (1.7%) temporarily discontinued study drug due to an AE.

No consistent trends or differences across the treatment groups were noted for clinical laboratory, ECG, or vital sign results.

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CONCLUSIONS:

- PF-00734200 was efficacious compared to placebo in reducing HbA1c at doses of 5 to 20 mg/day. The dose-response at Week 12 was monotonic with maximal predicted response of -0.75% over placebo.

- The administration of PF-00734200 did not yield meaningful changes from baseline to Week 12 in insulin AUC (0 to 180 minutes) following MMTT when compared to placebo. However, statistically significant changes were observed for the ratio of the insulin AUC (0 to 180 minutes) over glucose AUC (0 to 180 minutes) following MMTT for ≥5 mg/day PF-00734200 groups compared with the placebo group.

- A higher proportion of subjects meeting ADA HbA1c goals (defined as HbA1c <7%) were noted for all treatment groups ≥5 mg PF-00734200 versus placebo at Weeks 8 and 12. The odds of responses in these treatment groups were statistically significantly higher (p-value ≤0.05) compared to the odds of response in the placebo group.

- The addition of PF-00734200 to ongoing metformin therapy was well tolerated. The overall incidence of clinical AEs was similar in the treatment groups; however discontinuation due to AEs occurred only in the PF-00734200 groups. The most commonly occurring AEs in PF-00734200 subjects were upper respiratory tract infection and nasopharyngitis.

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