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

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS:

NCT NO.: 00618007

PROTOCOL NO.: A7941006

PROTOCOL TITLE: A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of 12-Week Administration of PF-00734200 to Subjects with Type 2 Diabetes Mellitus and Insufficient Glycemic Control on Metformin Treatment

Study Centers: The study was conducted at 84 centers (75 centers in the United States, 5 centers in Canada, and 4 centers in the Republic of Korea); 18 of these centers screened, but did not enroll subjects; thus, 66 centers enrolled subjects.

Study Initiation and Completion Dates: 01 February 2008 to 26 August 2008

Phase of Development: Phase 2

Study Objectives:

Primary Study Objective

- To evaluate the effect of 2 oral doses of PF-00734200 on change from Baseline to 12 weeks in hemoglobin A1c (HbA1c) levels in subjects with type 2 diabetes mellitus (T2DM) on metformin.

Secondary Objectives

- To evaluate the effect of 2 oral doses of PF-00734200 on change from Baseline to 12 weeks in fasting plasma glucose in subjects with T2DM on metformin.
- To compare the proportion of subjects who achieve the current American Diabetes Association (ADA) glycemic goal of HbA1c <7%.
- To provide 12-week safety and tolerability data of 2 oral doses of PF-00734200 in subjects with T2DM on metformin.

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Tertiary Objectives

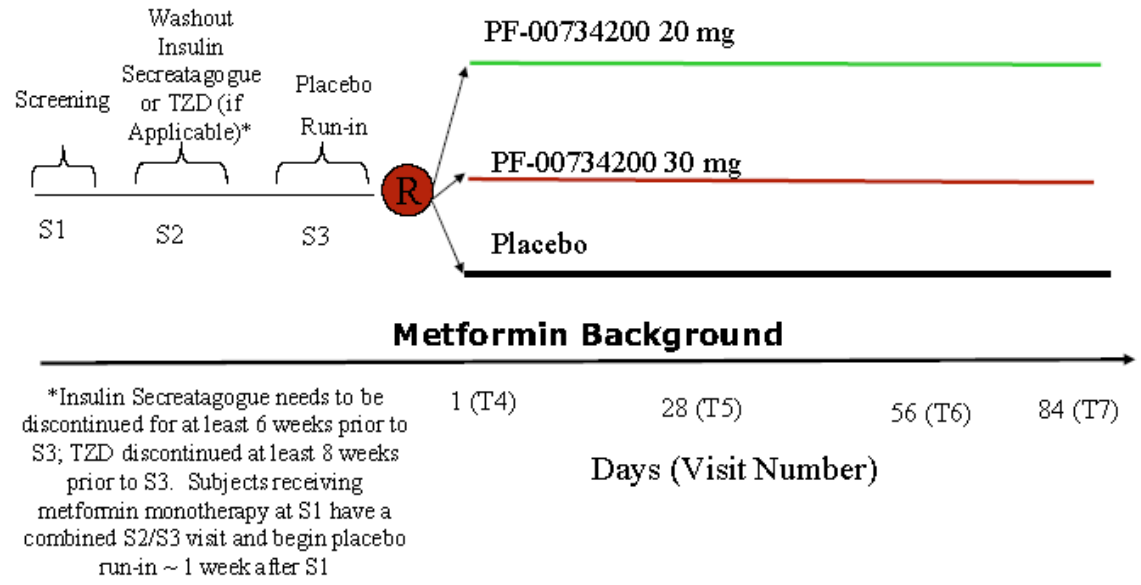
- To evaluate the effect of 2 oral doses of PF-00734200 on change from Baseline to 12 weeks in fasting insulin, proinsulin, and the proinsulin/insulin ratio.
- To evaluate the effect of 2 oral doses of PF-00734200 on change from Baseline to 12 weeks in homeostasis model assessment-B (HOMA-B) and HOMA-IR.
- To evaluate the effect of 2 oral doses of PF-00734200 on change from Baseline to 12 weeks in the fasting lipid profile.
- To characterize the pharmacokinetics (PK) of PF-00734200 in subjects with T2DM.

METHODS

Study Design: This was a multicenter, randomized, double-blind, placebo-controlled, multiple-dose, 3-arm, parallel-group study. A total of up to 7 clinic visits over a period of approximately 15-23 weeks were planned. Subjects were randomized to receive either placebo or PF-00734200 (at a dose of 20 mg/day or 30 mg/day).

The overall study design is summarized in Figure S1.

Figure S1. Study Design



Abbreviations: TZD= thiazolidinediones; S1=Screening Visit 1; S2=Screening Visit 2; S3=Screening Visit 3; R=randomization

The screening/eligibility run-in period was designed to allow subjects with T2DM on several different regimens at the Screening Visit 1 (S1) to participate. Men and women (aged 18-80 years at the time of S1) with T2DM were eligible to screen for this study if they were receiving the following glucose-lowering medications at the time of the S1 visit.

- Metformin monotherapy.
- Metformin + insulin secretagogue (IS; eg, sulfonylurea, meglitinide, or dipeptidyl peptidase-IV [DPP-IV] inhibitor); this had to be a single secretagogue (ie, subjects receiving combination therapy of metformin plus 1 additional agent).
- Metformin + thiazolidinediones (TZD; pioglitazone or rosiglitazone).

Table S1 provides information on the HbA1c inclusion criterion at Screening Visit 1 based on the background diabetes medication that the subject was receiving. All subjects must have been receiving a stable (ie, same daily) dose of metformin for at least 6 weeks prior to the Screening Visit (S1). There was no minimal metformin dose requirement for this study. Subjects continued to receive the same daily dose of metformin throughout the study.

Table S1. HbA1c Inclusion Criterion

Diabetes Medication at Screening Visit (S1)	HbA1c Inclusion Criterion	Change in Background Diabetes Medication
Metformin monotherapy	7.0-11.0%	None
Metformin + insulin secretagogue	6.5-9.5%, inclusive	Discontinue insulin secretagogue for at least 6 weeks prior to the placebo run-in visit.
Metformin + TZD	6.5-9.5%, inclusive	Discontinue TZD for at least 8 weeks prior to placebo run-in visit.

Abbreviations: HbA1c=hemoglobin A1c; TZD=thiazolidinediones; S1=Screening Visit

Number of Subjects (Planned and Analyzed): The planned number of subjects was 225 subjects in a 2:2:1 ratio. A total of 289 subjects were assigned to study treatment and were treated (57 placebo, 116 PF-00734200 20 mg, and 116 PF-00734200 30 mg). Of the 289 subjects who were treated, a total of 276 subjects were included in the Full Analysis Set (54 placebo, 112 PF-00734200 20 mg, and 110 PF-00734200 30 mg) and a total of 274 subjects were included in the Per Protocol Set (54 placebo, 110 PF-00734200 20 mg, and PF-00734200 30 mg). A total of 287 subjects were analyzed for safety (adverse event [AE] and laboratory data).

Diagnosis and Main Criteria for Inclusion: Subjects eligible for this study included males and females ≥18 and ≤80 years of age, with a body mass index of >22.0 and <45.0 kg/m^2, with a diagnosis of T2DM, in accordance with ADA guidelines. The subject's HbA1c at Screening Visit 1 was based on background diabetes medication and was to be 7.0-11.0% if the subject was on metformin monotherapy and was to be 6.5-9.5%, inclusive, if the subject was on metformin + IS or metformin + TZD.

Study Treatment: Approximately 225 subjects were planned to be randomized in a 2:2:1 ratio to receive 1 of the following treatment regimens: PF-00734200 20 mg orally (PO)

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once daily (QD) (90 subjects), and PF-00734200 30 mg PO QD (90 subjects), or placebo PO QD (45 subjects).

Efficacy Evaluations:

Efficacy evaluations included HbA1c, plasma glucose, insulin, proinsulin, and a lipid panel.

Pharmacokinetic and Pharmacodynamic Evaluations:

Pharmacokinetic Evaluations: Blood samples for PK analysis were collected on Days 28, 56, and 84 (or premature discontinuation) approximately 24 hours following the prior day's dosing and 0.75, 1.75, and 3.25 hours following the Day 84 dose (or last dose, if premature discontinuation) for measurement of serum PF-00734200.

Pharmacodynamic Evaluations: Pharmacodynamic evaluations included exploratory biomarkers related to the mechanism of action of PF-00734200. Samples were collected on Days 1 and 84 (or premature discontinuation). Note: Results for the banked biomarker samples will not be included in this study report as samples were not analyzed.

Safety Evaluations: Safety evaluations included physical examinations, clinical monitoring, AEs, safety laboratory tests, vital signs, and 12-lead electrocardiograms (ECGs).

Statistical Methods: The primary analysis population for all efficacy analysis included all subjects who were compliant with the dosing of randomized study medication and for whom there was a baseline observation and at least 1 postbaseline observation for the primary endpoint of HbA1c (Per Protocol Set). The Full Analysis Set consisted of all randomized subjects who received at least 1 dose of study medication and for whom there was a Baseline observation and at least 1 postbaseline observation for the primary endpoint of HbA1c during the treatment phase.

The primary endpoint of change from Baseline to Week 12 in HbA1c was analyzed by a linear model using analysis of covariance (ANCOVA) with terms for treatment and Baseline HbA1c. Least-squares (LS) means and 95% confidence intervals (CIs) were used to estimate the mean differences between each pair of treatment groups. All 3 pairwise comparisons among the 3 treatment groups were performed at a Type I error rate of 10%. Tukey-Kramer's testing procedure was used to adjust Type I error rate for the multiple comparisons. As a secondary analysis the primary endpoint was analyzed using the Full Analysis Set imputing the missing observations by a last observation carried forward methodology (LOCF).

Secondary and exploratory endpoints of changes from baseline in HbA1c, fasting plasma glucose, insulin, proinsulin, proinsulin/insulin ratio, HOMA-B, HOMA-IR and body weight were analyzed separately using the ANCOVA model adjusting for baseline values at Weeks 4 and 8 for HbA1c, Weeks 4, 8, and 12 for fasting plasma glucose and body weight, and Weeks 4 and 12 for all other endpoints. The proportion of subjects reaching HbA1c goal of <7% at Weeks 4, 8 and 12 was analyzed separately by a logistic regression model with terms for treatment and Baseline HbA1c. Lipid parameters were analyzed using rank-based

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regression of percent change from baseline with rank-transformed baseline value as a covariate.

In addition, consistency of treatment effects on HbA1c was examined across gender, age, race, Baseline HbA1c, body mass index (BMI), and metformin daily dose. Mean change from Baseline to Week 12 in HbA1c with 95% CIs of raw data was examined for the following categories (Table S2).

Table S2. Baseline Covariates and Categories for Examination of HbA1c

Baseline Covariate	Categories
Gender	Male, female
Age	<65 years, ≥65 years
Race	White, Black, Asian, Other
Baseline HbA1c (%)	<8.0, 8.0-8.9, ≥9
Body Mass Index (BMI)	<30, ≥30 kg/m^2
Metformin daily dose	≤1000 mg, >1000 mg
Geographic region	North America, Non-North America
Prior treatment regimen	metformin monotherapy, metformin + IS, metformin + TZD

Abbreviations: BMI=body mass index; HbA1c=glycosylated hemoglobin; IS=insulin secretagogue, TZD = thiazolidinediones
North America consisted of sites in United States, while Non-North America included sites in Canada and Korea.

Tertiary endpoints were analyzed using linear models. If the assumptions of the linear models were not satisfied, then nonparametric analysis using rank-regression was employed.

Pharmacokinetics: All pharmacokinetic 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.

RESULTS

Subject Disposition and Demography:

A summary of subject evaluation groups is provided in Table S3.

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Table S3. Subject Disposition

Number (%) of Subjects	Placebo n (%)	PF-00734200 20 mg n (%)	PF-00734200 30 mg n (%)
Screened: 622			
Treated	57	116	116
Completed	49 (86.0)	98 (84.5)	101 (87.1)
Evaluable for HbA1c at:			
Baseline	56 (98.2)	116 (100)	112 (96.6)
Week 4	53 (93.0)	104 (89.7)	108 (93.1)
Week 8	49 (86.0)	103 (88.8)	105 (90.5)
Week 12	43 (75.4)	95 (81.9)	94 (81.0)

Abbreviations: HbA1c=hemoglobin A1c; n=number of subjects

A summary of demographic characteristics is provided in Table S4.

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Table S4. Demographic Characteristics

Number (%) of Subjects	Placebo (N=57)	PF-00734200 20 mg (N=116)	PF-00734200 30 mg (N=116)
Gender, n (%)			
Male	26 (45.6)	54 (46.6)	65 (56.0)
Female	31 (54.4)	62 (53.4)	51 (44.0)
Age (years)			
Mean (SD)	56.1 (11.1)	56.8 (10.1)	56.5 (11.1)
Range	28-76	30-78	28-79
Race, n (%)			
White	47 (82.5)	88 (75.9)	88 (75.9)
Black	4 (7.0)	16 (13.8)	16 (13.8)
Asian	5 (8.8)	8 (6.9)	9 (7.8)
Other[a]	1 (1.8)	4 (3.4)	3 (2.6)
Ethnicity			
Hispanic/Latino	16 (28.1)	35 (30.2)	31 (26.7)
Non-Hispanic/Non-Latino	41 (71.9)	81 (69.8)	85 (73.3)
Weight (kg)			
Mean (SD)	89.1 (18.8)	89.6 (19.5)	91.0 (21.5)
Range	58.7-135.5	51.3-148.3	48.0-147.6
Body Mass Index			
Mean (SD)	32.4 (5.4)	32.2 (5.6)	32.2 (5.5)
Range	22.3-45.2	22.2-44.7	22.2-46.6

Abbreviations: N=number of subjects; n=number of subjects that met criteria; SD=standard deviations
[a] Other = Mexican (4 subjects), Egyptian (1 subject), Hispanic (1 subject), East Indian (1 subject), and American Indian (1 subject).

Efficacy Results:

- In this study in subjects with T2DM, statistically and clinically meaningful reductions from Baseline in HbA1c were achieved after 12 weeks of PF-00734200 20 mg or 30 mg added to metformin therapy. For the Per Protocol Set, the LS mean differences vs placebo were -0.79% (95% CI: -1.10, -0.49) and -0.92% (95% CI: -1.23, -0.61), for PF-00734200 20 mg and PF-00734200 30 mg, respectively, at Week 12. These results are consistent with those of the Full Analysis Population. The LS mean difference between 20 mg and 30 mg of PF-00734200 was -0.12%, which was not statistically significant.

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- The superiority of the PF-00734200 20 mg and 30 mg doses over placebo was observed as early as Week 4 and was sustained throughout the study.

- Subjects with higher baseline HbA1c values had higher reductions from Baseline in HbA1c at Week 12 across treatment groups. Additionally, prior treatment regimen also had an impact on the results; subjects on metformin monotherapy prior to entering the study had larger reductions from Baseline in HbA1c. No other differences were noted in the subgroups examined (eg, baseline metformin dose, BMI, age, race, gender, or geographic region).

- Both 20 mg and 30 mg doses of PF-00734200 were statistically significantly superior to placebo in reducing fasting plasma glucose from Baseline to Week 12. Placebo-adjusted LS mean reductions from Baseline of at least 18.0 mg/dL were noted for both PF-00734200 dose groups. The difference between 20 mg and 30 mg doses was not statistically significant. Results at Weeks 4 and 8 were consistent with the results at Week 12.

- A higher proportion of subjects meeting HbA1c goal of <7% were noted for both PF-00734200 20 mg and 30 mg doses vs placebo at Weeks 4, 8, and 12. The odds of responses (ie, HbA1c <7%) in these treatment groups were statistically significantly (p-value ≤0.05) vs the placebo group. The proportions of responders were 56%, 52%, and 24% for PF-00734200 20 mg and 30 mg, and placebo groups, respectively, at Week 12.

- There were statistically significant LS mean reductions in proinsulin from Baseline to Week 12 for PF-00734200 20 mg and to Week 4 and Week 12 for PF-00734200 30 mg vs placebo. The LS mean changes from Baseline to Week 12 for proinsulin were 1.19 uU/mL (95% CI: 0.29, 2.09), -0.37 uU/mL (95% CI: -1.00, 0.26), and -0.97 uU/mL (95% CI: -1.61, -0.34) for placebo, PF-00734200 20 mg, and PF-00734200 30 mg groups, respectively.

- There were no statistically significant changes from Baseline up to Week 12 for insulin, ratio of proinsulin/insulin, HOMA-B, HOMA-IR, lipid profile, or in body weight for either the 20 mg or 30 mg treatment groups.

Pharmacokinetic Results: Mean trough concentrations of PF-00734200 on 3 separate visits (Days 28, 56, and 84) were comparable with each dose, indicating that steady state had been reached by Day 28. Additionally, the mean concentrations were approximately proportional to dose.

Pharmacodynamic Results: Biomarker results for the banked samples will not be included in this study report as samples were not analyzed.

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Safety Results:

An overall summary of all-causality (treatment-related) treatment-emergent AEs is provided in Table S5 and a summary of all-causality (treatment-related) treatment-emergent AEs is provided in Table S6.

Table S5. Overall Summary of All-Causality Treatment-Emergent Adverse Events

Number (%) of Subjects	Placebo	PF-00734200 20 mg	PF-00734200 30 mg
Subjects evaluable for AEs	57	116	116
Number of AEs	33	80	108
Subjects with AEs	22 (38.6)	40 (34.5)	65 (56.0)
Subjects with SAEs	1 (1.8)	3 (2.6)	5 (4.3)
Subjects with severe AEs	1 (1.8)	6 (5.2)	8 (6.9)
Subjects discontinued due to AEs	1 (1.8)	2 (1.7)[a, b]	4 (3.4)
Subjects with dose reduced or temporarily discontinued due to AEs	2 (3.5)	2 (1.7)	1 (0.9)

Abbreviations: AE=adverse event; SAE=serious adverse event
Except for the Number of AEs, subjects were counted once per treatment in each row.
[a] This row does not include Subject 10261009, who discontinued the study due to protocol deviation in this table. The subject also was listed as discontinued due to an SAE (cellulitis) and is included in certain AE tables as discontinuing the study due to an AE. However, the actual reason for discontinuation for this subject was that a prohibited glucose-lowering agent was added to his treatment regimen during the hospitalization for cellulitis.
[b] This row does include Subject 10061007; however, the subject did not have thrombocytopenia, there was a laboratory error. The subject's Day 36 and Day 49 blood samples for platelet analysis were reported as "specimen unsuitable; platelet clumping". A repeat laboratory assessment performed on Day 63 at a local laboratory revealed a platelet count of 242 x $10^3/m^3$ (reference range, 130-450 x $10^3/m^3$). The subject did not have any AEs of bleeding during the study.

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Table S6. Treatment-Emergent Adverse Events Occurring in at Least 2 Subjects in Any Treatment Group

MedDRA (v11.0) preferred term	Placebo (N=57) n (%)	PF-00734200 20 mg (N=116) n (%)	PF-00734200 30 mg (N=116) n (%)
Total preferred term events	**33**	**80**	**108**
Arthralgia	0	2 (1.7)	1 (0.9)
Back pain	1 (1.8)	1 (0.9)	4 (3.4)
Blood creatine phosphokinase increased	0	1 (0.9)	2 (1.7)
Chest pain	0	0	2 (1.7)
Constipation	0	2 (1.7)	1 (0.9)
Diarrhea	1 (1.8)	1 (0.9)	4 (3.4)
Dizziness	0	2 (1.7)	1 (0.9)
Dyspepsia	0	3 (2.6)	0
Headache	1 (1.8)	3 (2.6)	1 (0.9)
Muscle spasms	0	0	2 (1.7)
Nasopharyngitis	1 (1.8)	2 (1.7)	2 (1.7)
Nausea	1 (1.8)	2 (1.7)	2 (1.7)
Nephrolithiasis	0	0	2 (1.7)
Pain in extremity	0	3 (2.6)	0
Peripheral edema	1 (1.8)	2 (1.7)	5 (4.3)[a]
Pharyngolaryngeal pain	0	3 (2.6)	0
Pruritus	0	2 (1.7)	2 (1.7)
Rash[b]	0	0	4 (3.4)
Sinusitis	0	2 (1.7)	0
Thrombocytopenia	0	2 (1.7)	0
Upper respiratory tract infection	2 (3.5)	1 (0.9)	2 (1.7)
Urinary tract infection	2 (3.5)	2 (1.7)	6 (5.2)[a]

Abbreviations: AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; v=version; N=number of subjects; n=number of subjects that met criteria
Subjects were counted only once per treatment in each row.
[a] 3/6 (50%) of these subjects with urinary tract infection and 2/5 (40%) of these subjects with peripheral edema had the AE beginning on Day 1.
[b] Rash=rash, rash macular, rash papular, and rash pruritic

There were some changes in laboratory test results that were considered related to study drug and that led to permanent discontinuation of study drug (thrombocytopenia [PF-00734200 20 mg], hyperglycemia [PF-00734200 30 mg], and blood creatinine increased [placebo]. There were no clinically significant findings in vital sign, ECG, or physical examination results.

CONCLUSIONS:

- PF-00734200 was efficacious compared to placebo in reducing HbA1c at both 20 mg and 30 mg doses. The difference between 20 mg and 30 mg was not statistically significant or clinically meaningful.
- PF-00734200 at doses of 20 mg and 30 mg was effective compared to placebo in reducing fasting plasma glucose.

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- A higher proportion of subjects treated with PF-00734200 20 mg and 30 mg achieved HbA1c <7% compared with subjects treated with placebo.

- PF-00734200 was safe and well-tolerated. The incidence of all causality AEs was similar for the placebo and 20 mg groups. However, the incidence of all causality AEs was higher in the 30 mg group compared to the 20 mg and placebo groups.

- Twelve weeks of treatment with PF-00734200 20 mg and 30 mg resulted in statistically significant decreases in the levels of proinsulin. However, there was no evidence of treatment effect on insulin and proinsulin/insulin ratio.

- There were no significant effects on HOMA-B or HOMA-IR.

- Treatment with PF-00734200 did not adversely impact the lipid profile or body weight.

- Mean trough serum concentrations of PF-00734200 on 3 separate visits (Days 28, 56, and 84) were comparable, and were approximately proportional to dose.

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