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COMPOUND NUMBER: PF-02393296

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: NA

NCT NO.: NA

PROTOCOL NO.: A8901002

PROTOCOL TITLE: A Randomized, Double-Blind, Placebo Controlled Single and Multiple Dose Escalation Study to Investigate the Pharmacokinetics, Safety and Tolerability of PF-02393296

Study Center: One center in Belgium

Study Initiation and Completion Dates: 31 March 2008 to 02 July 2008

Phase of Development: Phase 1

Study Objectives:

- To study the safety/tolerability of PF-02393296 following single and multiple doses.
- To study the pharmacokinetics of PF-02393296 following single and multiple doses.

METHODS

Study Design: This was a randomized, double-blind, third party (sponsor) open, placebo-controlled, escalating single and multiple dose study in 39 healthy male subjects. The study was run in 2 parts: Part 1, involving 9 subjects in Cohort 1, was a crossover design exploring escalating single doses of PF-02393296 using placebo substitution; Part 2, involving 10 subjects in each Cohorts 2 to 4, was a parallel design exploring escalating multiple doses of PF-02393296 with placebo (using a twice daily [BID] dosing regimen). Subjects were allocated to 1 of the 4 cohorts on the basis of their order of entry into the study.

Part 1: Cohort 1 was a 3-period, single dose escalation study with placebo substitution to establish the maximum tolerated dose. Nine subjects were randomized to receive a single, oral dose of either PF-02393296 (2000, 3000 or 4500 mg) or placebo (2:1 allocation ratio) in a 3-way placebo substitution design. Subjects received a high fat breakfast to be consumed within 30 minutes of administration of dose in each period.

For each subject the study consisted of up to 5 visits: a screening visit (within 28 days of first study drug administration), 3 treatment visits, and a follow-up visit (7 to 10 days after last study drug administration). Subjects were admitted to the clinical research unit (CRU) on the evening of Day 0 in each treatment period. Study treatment was administered on the morning of Day 1. Subjects remained resident in the CRU until after the 48-hour blood collection was made.

The dose for Periods 2 and 3 in Cohort 1 was selected based upon the safety/tolerability and pharmacokinetic profile at the preceding dose, and was not to exceed 4500 mg.

Part 2: Cohorts 2 to 4 had a parallel design to explore escalating multiple doses with placebo. Ten subjects were entered into each cohort and were randomized to either PF-02393296 (300, 1500 or 2500 mg) or placebo (4:1 allocation ratio).

For each subject the study consisted of a treatment visit (Day 0 to Day 11) and a follow-up visit (7 to 10 days after last study drug administration). Subjects were admitted to the CRU on the evening of Day 0. Administration of the first dose of PF-02393296 or placebo (Day 1) was 30 minutes after the start of a high fat breakfast, which was to be completed within 5 minutes before dosing. A second dose of study treatment was administered 24 hours after the first. Subjects then continued to receive study treatment BID until Day 9 (192 hours post first dose) receiving a total of 16 doses. Each dose was administered within 30 minutes of starting a meal and no more than 5 minutes after completion of the meal. Subjects remained in the CRU for safety profiling and blood sampling until 240 hours post first dose (ie, Day 11).

The doses for Cohorts 3 and 4 were selected based upon the safety/tolerability and pharmacokinetic profile of PF-02393296 in the single dose escalation and in the preceding multiple dose periods, and would not exceed 2500 mg.

Number of Subjects (Planned and Analyzed): It was planned to enroll 9 subjects for Cohort 1 (2:1 active:placebo) and 30 for Cohorts 2 to 4 (4:1 active:placebo). Nine subjects were randomized and received treatment in Cohort 1 and 10 subjects were randomized and received treatment in Cohorts 2 to 4.

Diagnosis and Main Criteria for Inclusion: Healthy male subjects between the ages of 18 and 55 years, inclusive, with a body mass index of approximately 18 to 30 kg/m^2; and a total body weight >50 kg (110 lbs); were included in the study.

Study Treatment: Subjects received the morning doses of study treatment between 07:00 and 10:00 hours following specified meal and diet restrictions. For Cohort 1, subjects received study treatment (PF-02393296 2000, 3000 or 4500 mg, or placebo) at approximately the same time for each study period. For Cohorts 2 to 4, Days 2-9, doses were administered BID at 12-hour intervals (PF-02393296 300, 1500 or 2500 mg, or placebo).

Oral doses consisted of an oral solution of total volume ≤450 mL. In order to standardize the conditions on pharmacokinetic sampling days, all subjects were required to refrain from

lying down (except when required for blood pressure, pulse rate, and ECG measurements), eating and drinking beverages other than water during the first 4 hours after dosing.

Efficacy Evaluations: No efficacy evaluations were done in this study.

Pharmacokinetic Evaluations: During all study periods, blood samples (4 mL) to provide a minimum of 2 mL plasma for pharmacokinetic analysis were collected into appropriately labeled tubes containing lithium heparin at the following times:

- Cohort 1: pre-dose then 1, 2, 4, 6, 8, 12, 16, 24, 36 and 48 hours post-dose for each period.

- Cohorts 2 to 4: pre-dose then 1, 2, 4, 6, 8, 12, 16, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, 193, 194, 196, 200, 204, 216, 228 and 240 hours post first dose, ensuring that the sample was taken pre-dose on Days 2 to 9 inclusive, for each cohort.

For Cohorts 2 to 4 only, urine was collected just prior to the 192 hour time point and from 192 to 204 hours post first dose.

Safety Evaluations: Safety evaluations consisted of adverse events (AEs), vital signs measurements, telemetry, 12-lead electrocardiograms (ECGs), physical examination findings, and blood and urine safety tests.

Statistical Methods: Cohort 1: Plasma pharmacokinetic parameters AUC_{inf}, C_{max}, AUC_{last}, AUC_{τ}, T_{max}, CL/F, Vz/F and $t_{½}$ were summarized descriptively by dose. Plasma concentrations were listed and summarized descriptively by nominal pharmacokinetic sampling time and dose. Individual subject and median profiles of the plasma concentration-time data were plotted by dose using actual and nominal times respectively. Median profiles were presented on both linear-linear and log-linear scales.

Dose normalized (to a 1 mg dose) AUC_{inf}, AUC_{last} and C_{max} were plotted against dose (using a logarithmic scale), and included individual subject values and the geometric means for each dose. The values were dose normalized by dividing the individual values and raw geometric means by dose.

Cohorts 2 to 4: Plasma pharmacokinetic parameters AUC_{last}, AUC_{inf}, AUC_{τ}, C_{max}, T_{max}, $t_{½}$, CL/F, Vz/F from Day 1 and AUC_{τ}, C_{max}, T_{max}, $t_{½}$ from Day 9 were summarized descriptively by dose. Plasma concentrations were summarized descriptively by dose, day and pharmacokinetic sampling time. Individual subject and median profiles of the plasma concentration-time data were plotted by dose and day (Days 1 and 9) using actual and nominal times respectively. Median profiles were presented on both linear-linear and log-linear scales.

Dose normalized (to a 1 mg dose) AUC_{inf} (AUC_{τ} at steady state), AUC_{last} and C_{max} were plotted against dose (using a logarithmic scale), as described for Cohort 1 parameters.

The observed accumulation ratio and the linearity ratio were summarized descriptively. Each was analyzed after natural log transformation using a 1-way analysis of variance with a single term for dose. The means and 90% confidence intervals (CIs) obtained from the model were back-transformed to provide means and 90% CIs for the accumulation and linearity ratios for each dose.

A median plot of the pre-dose concentrations against day was provided for each dose, on the same plot, in order to assess the attainment of steady-state. Individual subject profiles were also plotted.

Safety data were summarized using the sponsor's Data Standards. Data were tabulated, and presented by treatment group. No formal hypothesis testing was performed.

RESULTS

Nine subjects were randomized and received treatment in Cohort 1 and 30 subjects were randomized and received treatment in Cohorts 2 to 4 (Table S1). All subjects completed the study and were analyzed for safety. All subjects who received PF-02393296 were analyzed for pharmacokinetics.

Table S1. Subject Evaluation Groups – All Cohorts

Number of Subjects:	Cohort 1				Cohorts 2-4			
	PF-02393296			Placebo	PF-02393296			Placebo
	2000 mg	3000 mg	4500 mg		300 mg	1500 mg	2500 mg	
Assigned Study Treatment	N=9				N=30			
Treated	6	6	6	9	8	8	8	6
Completed	6	6	6	9	8	8	8	6
Discontinued	0	0	0	0	0	0	0	0
Analyzed for Pharmacokinetics								
Concentration	6	6	6	0	8	8	8	0
Parameter	6	6	6	0	8	8	8	0
Analyzed for Safety								
Adverse Events	6	6	6	9	8	8	8	6
Laboratory Data	6	6	6	9	8	8	8	6
Electrocardiogram	6	6	6	9	8	8	8	6
Vital Signs	6	6	6	9	8	8	8	6

Demographic data are summarized in Table S2. All subjects were healthy male adult volunteers aged between 20 and 54 years, inclusive. Demographic characteristics were consistent across treatment groups.

Table S2. Demographic Characteristics – All Cohorts

	Cohort 1	Cohorts 2 to 4			
	All Subjects	PF-02393296 300 mg	PF-02393296 1500 mg	PF-02393296 2500 mg	Placebo
	N=9	N=8	N=8	N=8	N=6
Age (years)					
Mean (SD)	30.6 (5.9)	35.3 (10.1)	32.6 (8.1)	25.6 (6.6)	35.3 (11.3)
Range	22-40	20-47	26-46	21-41	20-54
Body mass index (kg/m^2)					
Mean (SD)	25.6 (2.4)	25.1 (3.3)	26.5 (2.9)	23.1 (2.5)	24.9 (3.6)
Range	21.1-28.6	20.6-30.0	19.9-29.1	20.3-28.6	19.9-28.3
Race (n)					
White	7	7	7	6	5
Black	2	1	1	1	1

SD = Standard deviation

Pharmacokinetic Results:

No formal statistics were done to examine dose proportionality; however, dose normalized exposure parameters (such as C_{max} and AUC) provide an indication of this characteristic.

Single Dose Cohort 1: The mean terminal half-life measured for PF-02393296 after single dose administration ranged from 6.51 to 7.41 hours. Across the dose range studied T_{max} was constant, suggesting that there was no change in the rate of absorption of PF-02393296. Exposure (both C_{max} and AUC) increased less than proportionally with increasing dose. The decreasing values of dose normalized C_{max} and AUC with increasing PF-02393296 dose are suggestive of a sub-proportional response. A slight increase in both CL/F and Vz/F was seen with increasing dose (Table S3).

Table S3. Geometric Mean Plasma Pharmacokinetic Parameters – Cohort 1

	PF-02393296 2000 mg	PF-02393296 3000 mg	PF-02393296 4500 mg
	N=6	N=6	N=6
AUC_{last} (ng.hr/mL)	300435	419805	557446
Dose Normalized AUC_{last} (ng.hr/mL/mg)	150	140	124
AUC_{inf} (ng.hr/mL/mg)	310995	429010	566758
Dose Normalized AUC_{inf} (ng.hr/mL/mg)	156	143	126
C_{max} (ng/mL)	24536	34346	45306
Dose Normalized C_{max} (ng/mL/mg)	12.3	11.5	10.1
T_{max}[a] (hr)	4.0	4.0	4.0
$t_{½}$[b] (hr)	6.5	6.9	7.4
CL/F (L/hr)	6.43	6.99	7.92
Vz/F (L)	60.2	69.3	83.6

[a] Median
[b] Arithmetic mean

Single Dose Cohorts 2 to 4 (Day 1): There was little difference in the mean terminal half-life measured for PF-02393296 after single dose administration; respective values following 300, 1500 and 2500 mg were 6.05, 6.04 and 6.26 hours. The rate of absorption appeared constant across the dose range studied; the observed median T_{max} was 4 hours postdose at each dose. C_{max} appeared to be slightly less than dose proportional, as suggested by the dose normalized C_{max} which declined at higher doses. From PF-02393296 300 to 2500 mg there was a reasonable dose proportional increase in AUC_{inf} (Table S4).

Table S4. Geometric Mean Plasma Pharmacokinetic Parameters – Single Dose Cohorts 2 to 4 (Day 1)

	PF-02393296 300 mg N=8	PF-02393296 1500 mg N=8	PF-02393296 2500 mg N=8
AUC_{inf} (ng.hr/mL)	49534	248618	400497
Dose Normalized AUC_{inf} (ng.hr/mL/mg)	165	166	160
AUCτ (ng.hr/mL)	35915	166448	271376
C_{max} (ng/mL)	4461	19541	31621
Dose Normalized C_{max} (ng/mL/mg)	14.9	13.0	12.7
T_{max} [a] (hr)	4.0	4.0	4.0
$t_{½}$ [b] (hr)	5.7	6.5	6.2
CL/F (L/hr)	6.05	6.04	6.26
Vz/F (L)	48.0	56.6	55.3

[a] Median
[b] Arithmetic mean

Multiple Dose Cohorts 2 to 4 (Day 9): Overall, dose normalized exposure data suggested that dose proportionality was reasonably maintained for both AUC_{inf} and C_{max} across the dose range investigated. Plasma concentrations were at steady state on Day 9. The mean terminal half-life (measured on Day 9 during washout from steady state) ranged from 6.68 to 7.27 hours (Table S5). Accumulation of PF-02393296 upon multiple dosing was consistent and limited across the dose range studied; the estimated $R_{ac(obs)}$ values for the 300, 1500 and 2500 mg doses were 1.47 (90% CI: 1.41, 1.54), 1.51 (90% CI: 1.45, 1.57) and 1.52 (90% CI: 1.45, 1.58) respectively. Furthermore linearity was conserved upon multiple dosing; the estimated Rss values for the 300, 1500 and 2500 mg doses were 1.07 (90% CI: 1.01, 1.13), 1.01 (90% CI: 0.96, 10.7) and 1.03 (90% CI: 0.98, 1.09) respectively.

Table S5. Geometric Mean Plasma Pharmacokinetic Parameters – Multiple Dose Cohorts 2 to 4 (Day 9)

	PF-02393296 300 mg N=8	PF-02393296 1500 mg N=8	PF-02393296 2500 mg N=8
AUC_{inf} (ng.hr/mL)	76750	375586	625539
Dose Normalized AUC_{inf} (ng.hr/mL/mg)	256	250	250
AUCτ (ng.hr/mL)	52905	250950	411323
C_{max} (ng/mL)	6136	28102	45747
Dose Normalized C_{max} (ng/mL/mg)	20.5	18.7	18.3
T_{max}[a] (hr)	4.0	4.0	4.0
$t_{½}$[b] (hr)	6.68	7.27	7.09

[a] Median
[b] Arithmetic mean

Safety Results: There were no deaths, serious AEs or discontinuations due to AEs reported in this study. The incidence of AEs was comparable across the PF-02393296 and placebo treatment groups during both parts of the study. All AEs reported during the study were mild or moderate in intensity. The most commonly reported all causality AEs in Cohort 1 were tooth fracture and nasal congestion, each of which were reported by 3 subjects in total. No individual AE was reported by more than 1 subject in any treatment group and the majority of AEs were considered by the investigator not to be related to study treatment. The most commonly reported AEs in Cohorts 2 to 4 were headache and diarrhea, each of which were reported by 6 subjects in total. Five of the 6 subjects reporting headache were receiving PF-02393296 (4 subjects on 1500 mg and 1 subject on 2500 mg) and 3/6 subjects reporting diarrhea were receiving placebo. There were no AEs reported in the PF-02393296 300 mg group. All AEs in Cohorts 2 to 4 were considered by the investigator to be treatment-related.

There were no clinically significant changes in laboratory, vital signs or ECG data.

Conclusions: PF-02393296 was well tolerated across the whole dose range tested in this study. The incidence of AEs was comparable across the PF-02393296 and placebo treatment groups during both parts of the study. All AEs reported during the study were mild or moderate in intensity. The most commonly reported all causality AEs were tooth fracture and nasal congestion in Cohort 1, and headache and diarrhea in Cohorts 2 to 4. There were no clinically significant changes in laboratory, vital signs or ECG data.

T_{max} was consistent following single oral doses of PF-02393296. AUC parameters and C_{max} increased slightly less than dose proportionally although $t_{½}$ was similar across all doses.

Following multiple dosing (300 to 2500 mg BID) there was minimal accumulation of PF-02393296, which was consistent with the measured half-life of around 6 to 7 hours. Additionally pharmacokinetic linearity was conserved. Although dose proportionality was not formally tested statistically, evaluation of the dose normalized exposure parameters, AUC and C_{max}, suggested that it was likely to be reasonably maintained across the dose range studied.