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COMPOUND NUMBER: PF-03635659

PROTOCOL NO.: B0431010

PROTOCOL TITLE: A Phase 2a, Double-Blind, Placebo-Controlled, Single Dose, 5-Way Crossover Study Assessing the Pharmacodynamic, Pharmacokinetic and Safety Profiles of Oral Inhaled PF-03635659 in Patients With Moderate Chronic Obstructive Pulmonary Disease

Study Centers: One center in Germany took part in the study and randomized subjects.

Study Initiation and Final Completion Dates: 15 February 2010 to 15 June 2010

Phase of Development: Phase 2a

Study Objectives:

Primary Objectives:

- To estimate the bronchodilatory trough effect of 3 single dose levels of PF-03635659 delivered via the CRC749 inhaler device in moderate chronic obstructive pulmonary disease (COPD) subjects in order to select the lowest efficacious dose to study in Phase 2b;

- To investigate the pharmacokinetics (PK) of 3 single dose levels of PF-03635659 delivered via the CRC749 inhaler device in moderate COPD subjects.

Secondary Objectives:

- To 'bench mark' the efficacy trough effect of single dose PF-03635659 against single dose Spiriva (tiotropium bromide) 18 μg;

- To investigate the safety and toleration of 3 single dose levels of PF-03635659 delivered via the CRC749 inhaler device in moderate COPD subjects.

METHODS

Study Design: This was a double-blind, double-dummy, third party open (ie, the subjects and Investigator were blinded, but the Sponsor was not), 5 way crossover, placebo-controlled study to determine the efficacy and PK of PF-03635659 in moderate COPD subjects using tiotropium bromide 18 μg (referred to as tiotropium in this report) as the positive control.

Each subject was to receive 3 single doses of PF-03635659 (180, 580 or 1450 μg; fine particle dose [FPD] 40, 128 or 320 μg, respectively), placebo, and tiotropium 18 μg over 5 study periods (1 treatment per period) with a washout between each period.

Subjects were to attend the Clinical Research Unit (CRU) on 7 occasions consisting of a Screening visit (up to 28 days prior to start of dosing in Treatment Period 1), 5 study periods and a Follow-up visit. During each of the study periods, subjects were admitted on the day prior to dosing (Day 0) and remained until completion of the 48 hour postdose assessments on Day 3. Study periods were to be separated by at least 7 days. The Follow-up visit was to be completed at least 7 days after the final study period.

The schedule of activities is presented in Table 1.

An interim analysis was planned to be performed after 10 subjects had completed all 5 periods. The sample size was to be re-estimated and the data analyzed. Following the sample size re-estimation, up to a further 15 subjects were to be enrolled to complete the study. If the primary efficacy objective was already met at the interim, the study was to still continue to increase precision on the comparison of PF-03635659 doses to tiotropium.

Table 1. Schedule of Activities

Protocol Activity	Screen	Study Periods 1-5																	Follow-Up
		Day 0	Day 1											Day 2				Day 3	
			Predose		Dose	Postdose													
			1 h	30 min		30 min	1 h	2 h	4 h	6 h	8 h	10 h	12 h	16 h	24 h	24.5 h	36 h	48 h	
Informed consent	X																		
Admission to clinic		X																	
Medical history	X	X																	
Physical examination (full)	X																		
Physical examination (brief)		X																X	X
Safety laboratory	X	X																	X
FSH[a]	X																		
Urine drug test	X	X																	
Alcohol breath test	X	X																	
ECG	X[b]		X[c]				X[b]	X[b]	X[b]		X[b]				X[b]				X[b]
Supine and standing BP and PR	X		X				X	X	X		X		X		X				X
Ipratropium 40 µg administration	X																		
Spirometry	X[d]		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK blood sampling			X			X	X	X	X		X		X		X		X	X	
Retained blood sample			X[e]																
Study treatment administration					X														
Discharge from clinic																		X	
Concomitant medication	X----------																		----------X
AE monitoring		X----------																	----------X

AE = adverse event; BP = blood pressure; ECG = electrocardiogram; FSH = follicle stimulating hormone; PR = pulse rate; PK = pharmacokinetic; Screen = screening.

a. This test was for females, aged 40 to 65 years, who had been amenorrheic for >2 years.
b. Single measure.
c. Triple measure.
d. Single measure before dosing with ipratropium 40 µg and triple measure 45 to 60 minutes post dosing with ipratropium 40 µg.
e. Period 1 only.

Number of Subjects (Planned and Analyzed): The total number of subjects planned for the study was not to exceed 25 subjects. A total of 22 subjects were assigned to study treatment.

Diagnosis and Main Criteria for Inclusion: Male or female (women of non-childbearing potential) subjects between the ages of 40 and 80 years inclusive, with a diagnosis of moderate COPD and who met the criteria for Global Initiative for Obstructive Lung Disease Stage II disease, with a body mass index of <35.5 kg/m^2 and a total body weight >40 kg (88lbs). Subjects had to be current smokers, or ex-smokers who had abstained from smoking for at least 6 months. Subjects had to have stable disease for 1 month prior to Screening and to be able to manage their disease with short-acting bronchodilators.

Exclusion Criteria: Subjects having >2 exacerbations requiring treatment with oral steroids or hospitalization for the treatment of COPD in the previous year or with a history of lower respiratory tract infection or significant disease instability during the month preceding Screening or during the period between Screening and Randomization were excluded from the study.

Study Treatment: Subjects were assigned to receive 3 single doses of PF-03635659 (180, 580 or 1450 μg; FPD 40, 128 or 320 μg, respectively), placebo and tiotropium 18 μg over 5 study periods (1 treatment per period).

Tiotropium or tiotropium placebo was administered via inhalation using the Handihaler. PF-03635659 or PF-03635659 placebo was administered via the CRC749 inhaler device. Subjects were thoroughly trained in the use of each device and their administration was guided and supervised by staff at the CRU to ensure compliance. Doses were administered in a standing position.

At Screening, ipratropium 40 μg (Atrovent) was administered using a metered dose inhaler, with or without the use of a spacer device, or dry powder inhaler, according to subject preference.

PF-03635659 and placebo for PF-03635659 dry powder for inhalation were presented in 2 CRC749 inhaler devices, which contained either 45 μg per inhalation, 145 μg per inhalation or placebo. Tiotropium and placebo for tiotropium were presented as a capsule dosage form to be used with the Handihaler device.

The dosing administration schedule to achieve the 5 treatments each subject received is detailed in Table 2.

Table 2. PF-03635659 Nominal Doses, Tiotropium and Matching Placebo Doses

	Number of Inhalations		
Dose	**Handihaler Device**	**CRC749 Inhaler Device 1**	**CRC749 Inhaler Device 2**
Placebo	1 (placebo)	4 (placebo)	6 (placebo)
PF-03635659 180 µg	1 (placebo)	4 (45 µg dose)	6 (placebo)
PF-03635659 580 µg	1 (placebo)	4 (145 µg dose)	6 (placebo)
PF-03635659 1450 µg	1 (placebo)	4 (145 µg dose)	6 (145 µg dose)
Tiotropium	1 (18 µg dose)	4 (placebo)	6 (placebo)

Nominal doses of 180, 580, and 1450 µg correspond to fine particle doses of 40, 128, and 320 µg, respectively.

Efficacy, Pharmacokinetic, Pharmacodynamic and Safety Endpoints:

Primary Endpoints:

- Change from Baseline in trough forced expiratory volume in 1 second (FEV_1);
- Maximum observed concentration (C_{max}), C_{max} normalized for FPD ($C_{max[dn1]}$), time for C_{max} (T_{max}), area under the plasma concentration time profile from time 0 to the time of the last quantifiable concentration (C_{last}) (AUC_{last}), AUC_{last} normalized for FPD ($AUC_{last[dn1]}$), area under the plasma concentration time profile from time 0 extrapolated to infinite time (AUC_{inf}), AUC_{inf} normalized for FPD ($AUC_{inf[dn1]}$), and terminal half-life ($t_{½}$).

Secondary Endpoints:

- Peak FEV_1 (maximum change from Baseline in FEV_1);
- Weighted average FEV_1 response (defined as the average area under the effect curve [AUEC] change from baseline FEV_1 - the area under the FEV_1 effect curve over 24.5 hours postdose for each study period, divided by 24.5);
- Forced vital capacity (FVC);
- Inspiratory capacity (IC);
- Adverse events (AEs), blood pressure (BP), pulse rate, and electrocardiograms (ECGs).

Safety Evaluations: Safety evaluations included AE monitoring, vital signs (pulse rate and BP), 12-lead ECGs, physical examination, and safety laboratory tests.

Statistical Methods: The following analysis populations were defined in the study:

- Full Analysis Set (FAS): The FAS included all subjects randomized and who received at least 1 dose of randomized treatment.
- The Efficacy Analysis Set (EAS): The EAS, a subset of the FAS, used for sensitivity analysis was defined as follows: included only subjects who had at least 1 valid FEV_1 measurement in at least 1 treatment period; did not include any FEV_1 data for a given

period, where a subject had received rescue medication for COPD within 6 hours prior to study drug dosing; did not include FEV_1 data taken up to 6 hours after the use of rescue medication for COPD within a treatment period; did not include FEV_1 data taken within 2 weeks of receiving long-acting β_2 agonist/tiotropium; did not include FEV_1 data from a treatment period that was within 7 days of previous dose administered; did not include any subject who had a change of ≥35% between minimum and maximum baseline FEV_1 measurements, calculated as a percentage of the minimum measurement.

- Safety Analysis Set: The safety analysis set included all subjects who received at least 1 dose of study treatment.

- PK Concentration Analysis Set: The PK concentration analysis set included all subjects randomized and treated who had at least 1 concentration in at least 1 study treatment period.

- PK Parameter Analysis Set: The PK parameter analysis set included all subjects randomized and treated who had at least 1 of the PK parameters of interest in at least 1 study treatment period.

The primary analysis was based on the FAS excluding influential outliers and the primary endpoint was the change from Baseline in trough FEV_1 for comparisons to placebo and tiotropium. For each treatment period, Baseline was defined as the average of the 2 predose readings and trough was defined as the average of the 24 and 24.5 hours postdose measurements. Peak FEV_1 was defined as the maximum observed change from Baseline in postdose reading within 48 hours. Weighted average change was calculated as an area under the change from Baseline effect curve (AUEC): area was estimated using the linear trapezoidal rule.

The data were analyzed using a maximum effect (E_{max}) model. A random term was used to describe the between-subject variability. Period was fitted as a fixed effect, together with 2 baseline covariates to separate out the effect of baseline between- and within-subjects. The tiotropium effect was modeled on the same E_{max} curve as PF-03635659 by adding a covariate to the median effective dose (ED_{50}, ie, dose that produces 50% of E_{max}) parameter, thus allowing a different ED_{50} for tiotropium. The predicted mean FPD was used to model the response against dose to reflect more appropriately the expected inhaled dose.

A Bayesian interpretation was applied to the results with a non-informative design prior assumed.

The comparisons of interest were:

- PF-03635659 180 μg – Placebo;

- PF-03635659 580 μg – Placebo;

- PF-03635659 1450 μg – Placebo;

- Tiotropium 18 μg – Placebo;
- PF-03635659 180 μg – Tiotropium 18 μg;
- PF-03635659 580 μg – Tiotropium 18 μg;
- PF-03635659 1450 μg – Tiotropium 18 μg.

The estimated E_{max} parameter and associated standard error (SE) of this parameter was used to calculate P1, the probability of all treatment effects being superior to placebo:

- P1: probability of all treatment effects (E_{max}) being >0.

For each of the comparisons to placebo, the predicted mean effect and associated SE of this difference were used to calculate:

- P2: probability of the effect being >0.1 L.

End of study success was defined as a P1 of 0.9 or more and a P2 of 0.2 or more.

To support the interpretation of the primary analysis, an identical analysis as described above, based on the EAS, was conducted.

Peak FEV_1 and weighted average FEV_1 were analyzed using a mixed effects analysis of variance (ANOVA) model. The effect of FEV1 over time was analyzed using a repeated measures analysis. Other spirometry endpoints (FVC, IC) were summarized using descriptive statistics only.

Interim Analysis: A planned interim analysis was conducted when 10 subjects had completed the study. There were 3 main purposes of the statistical interim: to assess futility on change from Baseline in trough FEV_1, to assess clear efficacy on change from Baseline in trough FEV_1 and to re-estimate the sample size from the estimated intra-subject variability.

To assess the relationship between PK parameters and dose, dose normalized 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 relative to 1 μg FPD.

RESULTS

Subject Disposition and Demography: A total of 22 subjects were assigned to study treatment and were treated (Table 3). One (1) subject was discontinued due to a treatment related AE (mild atrial flutter) after receiving tiotropium 18 μg in Period 4, and consequently did not receive the final assigned treatment (PF-03635659 1450 μg) in Period 5. All 22 subjects were included in the FAS. A total of 3 subjects were excluded from the EAS as they had changes of ≥35% between minimum and maximum baseline FEV_1 measurements. All subjects treated with PF-03635659 or tiotropium were analyzed for PK under the treatment received.

Table 3. Subject Evaluation Groups

	PF-03635659 180 µg	PF-03635659 580 µg	PF-03635659 1450 µg	Tiotropium 18 µg	Placebo
Assigned to treatment (N=22)					
Treated	22	22	21	22	22
Completed	22	22	21	21	22
Discontinued	0	0	0	1	0
Related to study drug	0	0	0	1	0
AE	0	0	0	1	0
Analyzed for PK					
Parameter	22	22	21	0	0
Concentration	22	22	21	22	0
Analyzed for efficacy					
FAS	22	22	21	22	22
EAS	19	19	19	19	19
Analyzed for safety					
AE	22	22	21	22	22
Laboratory data	22	22	21	22	22

AE = adverse event; EAS = efficacy analysis set; FAS = full analysis set; N = number of subjects; PK = pharmacokinetics.

Demographic characteristics are summarized in Table 4. Subjects were between the ages of 42 and 76 years (mean age: 58.7 years). Of the total 22 subjects, 16 were male and 6 were female. All subjects fulfilled the moderate COPD criteria for post-bronchodilator FEV_1 and FVC.

Table 4. Summary of Demographic Characteristics

	All Subjects
Total number of subjects	22
Age (years)	
Mean (SD)	58.7 (9.3)
Range	42-76
Weight (kg)	
Mean (SD)	79.1 (12.6)
Range	56.0-104.6
Body mass index (kg/m^2)	
Mean (SD)	26.7 (3.3)
Range	18.3-33.8

SD = standard deviation.

Efficacy, Pharmacokinetic and Pharmacodynamic Results:

Change From Baseline Trough FEV_1: Results of the primary analysis are presented in Table 5 (comparison to placebo) and Table 6 (comparison to tiotropium). The mean (± SE) differences from placebo were 50.7 (±33.9), 78.8 (±27.0) and 92.7 (±27.7) mL for the 180, 580 and 1450 µg doses of PF-03635659, respectively, and 61.3 (±30.0) mL for tiotropium 18 µg. There was >99% probability that the E_{max} parameter was >0 (mean [SE] of 105 mL [39.5]) and therefore >99% probability that all active treatment arms were superior to placebo (Table 5). The 580 and 1450 µg doses of PF-03635659 had >20% probability that the effect over placebo was ≥100 mL. PF-03635659 180 µg and tiotropium 18 µg had a 10 and 13% probability, respectively, of achieving the 100 mL target size in this study.

Table 5. Primary Analysis: E_{max} Model - Change From Baseline in Trough FEV_1 (Comparison to Placebo) – FAS[a]

Comparison	Estimate (L)	SE	CI[b]	P1	P2
PF-03635659 180 µg – Placebo	0.0507	0.0339	0.0059-0.0798	0.996	0.098
PF-03635659 580 µg – Placebo	0.0788	0.0270	0.0431-0.1019	0.996	0.260
PF-03635659 1450 µg – Placebo	0.0927	0.0277	0.0560-0.1166	0.996	0.425
Tiotropium 18 µg – Placebo	0.0613	0.0300	0.0215-0.0871	0.996	0.133

Nominal doses of 180, 580, and 1450 µg correspond to FPD of 40, 128, and 320 µg, respectively.
CI = credible interval; E_{max} = maximum effect; FAS = full analysis set; FEV_1 = forced expiratory volume in 1 second; FPD = fine particle dose; P1 = probability that all treatment effects >0; P2 = probability that effect was >0.1 L; SE = standard error.

a. Excluding influential outliers. Any observation with a raw residual greater than ±0.3 L was considered as an influential outlier and therefore excluded from the analysis.
b. The lower CI was a 1–sided 90% CI and the upper CI was a 1–sided 80% CI.

PF-03635659 doses were also compared to tiotropium 18 µg using the same E_{max} model. The 3 dose levels of PF-03635659 showed mean (± SE) differences from tiotropium of -10.5 (±30.9), 17.5 (±24.6) and 31.5 (±29.4) mL for 180, 580 and 1450 µg, respectively (Table 6). Based on this analysis, PF-03635659 580 µg and 1450 µg have approximately 80% probability of having a greater effect on trough FEV_1 than tiotropium 18 µg.

Table 6. Primary Analysis: E_{max} Model - Change From Baseline in Trough FEV_1 (Comparison of PF-03635659 to Tiotropium) – FAS[a]

Comparison	Estimate (L)	SE	CI[b]
PF-03635659 180 µg – Tiotropium 18 µg	-0.0105	0.0309	-0.0371
PF-03635659 580 µg – Tiotropium 18 µg	0.0175	0.0246	-0.0037
PF-03635659 1450 µg – Tiotropium 18 µg	0.0315	0.0294	0.0062

CI = credible interval; E_{max} = maximum effect; FAS = full analysis set; FEV1 = forced expiratory volume in 1 second; FPD = fine particle dose; SE = standard error.

a. Excluding influential outliers. Any observation with a residual greater than ±0.3 L was considered as an influential outlier and therefore excluded from the analysis.

b. Lower 1–sided 80% CI.

Pharmacokinetic Results: PK parameter values are summarized in Table 7 AUC_{inf} and $t_{½}$ could not be calculated or reported for most of the profiles across all dose groups due to the very low plasma concentrations. These have therefore not been reported.

Following administration of single oral inhalation doses of PF-03635659 at nominal doses of 180, 580 and 1450 µg (FPD of 40, 128 and 320 µg, respectively) absorption was rapid. C_{max} occurred approximately 0.417 to 3.95 hours postdose (median T_{max} 0.467 to 0.950) and plasma levels declined gradually over time with low but measurable PF-03635659 levels in a small number of subjects at 4 hours (2 out of 22 subjects), 12 hours (1 out of 16 subjects), and 24 hours (5 out of 21 subjects) postdose, for the 180, 580 and 1450 µg dose groups, respectively.

For the 180 µg low dose group, only 9 out of 22 subjects had sufficient plasma concentrations (at least 3 consecutive plasma concentrations) above the limit of detection to calculate accurate AUC_{last} values. Because AUC_{last} parameters could not be calculated for 13 out of 22 subjects (>50%), geometric mean values for AUC_{last} were not reported for the 180 µg dose group.

Overall, PF-03635659 exposure as measured by AUC_{last} and C_{max} increased with an increase in dose from 580 to 1450 µg with geometric mean AUC_{last} values of 598.4 pg•hr/mL and 2513 pg•hr/mL for the 580 and 1450 µg dose groups, respectively, and geometric mean C_{max} values of 53.21, 169.4, and 471.2 pg/mL for the 180, 580 and 1450 µg dose groups, respectively.

Approximately a 4-fold increase in geometric mean AUC_{last} values was observed for a 3-fold increase in dose between the 580 and the 1450 µg dose with dose proportional increases in mean geometric C_{max} values across all doses. Inter-subject variability in PF-03635659 exposure (AUC_{last} and C_{max}) based on coefficients of variation ranged between 34% to 76%.

Table 7. Summary of Plasma PF-03635659 Pharmacokinetic Parameter Values

Parameter, Units	Parameter Summary Statistics [a] by PF-03635659 Treatment		
	180 µg (40 µg FPD)	580 µg (128 µg FPD)	1450 µg (320 µg FPD)
N, n	22, 22	22, 22	21, 21
AUC_{last}, pg•hr/mL	NC	598.4 (49)	2513 (50)
C_{max}, pg/mL	53.21 (76)	169.4 (34)	471.2 (40)
T_{max}, hr	0.533 (0.433-1.93)	0.950 (0.433-3.95)	0.467 (0.417-1.95)
	PF-03635659 Parameters Normalized to a 1 µg FPD		
AUC_{last}(dn1), pg•hr/mL/µg	NC	4.676 (49)	7.856 (50)
C_{max} (dn1)[b], pg/mL/µg	1.331 (76)	1.323 (34)	1.474 (40)

AUC_{last} = area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (Clast); C_{max} = maximum observed concentration; dn1 = parameter dose normalized to a 1 µg FPD (40, 128, and 320 µg for the nominal doses of 180, 580, and 1450 µg, respectively); FPD = fine particle dose; N = number of subjects in the treatment group; n = number of subjects contributing to the mean; NC = not calculated for any subjects in the treatment group; T_{max} = time for C_{max}.

a. Geometric mean (%CV) for AUC_{last} and AUC_{last} (dn1), C_{max} and C_{max} (dn1); median (range) for T_{max}.

b. Zero values have been replaced by 25 pg/mL (1/2 of the lower limit of detection for the calculation of geometric mean of C_{max} and by 25/FPD pg/mL/µg (where FPD = 40, 128, 320 respectively) for the calculation of geometric mean of C_{max} (dn1).

Peak FEV_1 – Change From Baseline: Peak FEV_1 was analyzed using an ANOVA model. Results are shown in Table 8 (comparisons to placebo) and Table 9 (comparisons to tiotropium). As seen for trough FEV_1, there was a clear dose response relationship of PF-03635659 on change from Baseline peak FEV_1. All active treatment arms showed a high probability (>90%) of superiority to placebo on this endpoint. Compared to tiotropium 18 µg, PF-03635659 580 µg and 1450 µg have approximately 80% probability of having a greater effect on peak FEV_1 than the positive control.

Table 8. Secondary Analysis: ANOVA Model - Change From Baseline in Peak FEV_1 (Comparison to Placebo) - FAS[a]

Comparison	Estimate (L)	SE	CI[b]
PF-03635659 180 µg – Placebo	0.0989	0.0242	0.0676
PF-03635659 580 µg – Placebo	0.1748	0.0245	0.1431
PF-03635659 1450 µg – Placebo	0.1909	0.0243	0.1594
Tiotropium 18 µg – Placebo	0.1528	0.0237	0.1222

Period and 2 baseline covariates were considered as fixed effects, subject was considered as a random effect.
PF-03635659 doses 180, 580 and 1450 µg correspond to FPD 40, 128 and 320 µg, respectively.
ANOVA = analysis of variance; CI = credible interval; FAS = full analysis set; FPD = fine particle doses; FEV1 = forced expiratory volume in 1 second; SE = standard error.

a. Excluding influential outliers. Any observation with a studentized residual greater than ±3 was considered as an influential outlier and therefore excluded from the analysis.

b. Lower 1–sided 90% CI.

Table 9. Secondary Analysis: ANOVA Model - Change From Baseline in Peak FEV_1 (Comparison of PF-03635659 to Tiotropium) - FAS[a]

Comparison	Estimate (L)	SE	CI[b]
PF-03635659 180 µg – Tiotropium 18 µg	-0.0539	0.0239	-0.0849
PF-03635659 580 µg – Tiotropium 18 µg	0.0220	0.0238	-0.0088
PF-03635659 1450 µg – Tiotropium 18 µg	0.0381	0.0242	0.0068

Period and 2 Baseline covariates were considered as fixed effects, subject was considered as a random effect.
PF-03635659 doses 180, 580 and 1450 µg correspond to FPD 40, 128 and 320 µg, respectively.
ANOVA = analysis of variance; CI = credible interval; FAS = full analysis set; FPD = fine particle doses; FEV1 = forced expiratory volume in 1 second; SE = standard error.

a. Excluding influential outliers. Any observation with a studentized residual greater than ±3 was considered as an influential outlier and therefore excluded from the analysis.
b. Lower 1–sided 80% CI.

In the analysis of weighted average FEV_1 using an ANOVA model, PF-03635659 showed a clear dose response relationship. All active treatment arms showed a high probability (>90%) of superiority to placebo (Table 10). Compared to tiotropium 18 µg, PF-03635659 180 µg showed a lower effect while the 580 and 1450 µg doses had an effect similar to tiotropium (Table 11).

Table 10. Secondary Analysis: ANOVA Model - Change From Baseline in Weighted Average FEV_1 (Comparison to Placebo) - FAS[a]

Comparison	Estimate (L)	SE	CI[b]
PF-03635659 180 µg – Placebo	0.0852	0.0214	0.0576
PF-03635659 580 µg – Placebo	0.1418	0.0219	0.1136
PF-03635659 1450 µg – Placebo	0.1692	0.0216	0.1413
Tiotropium 18 µg – Placebo	0.1526	0.0212	0.1252

Weighted average FEV_1 response was defined as the AUEC change from baseline FEV_1, divided by 24.5 hours. AUEC was defined as the area under the FEV_1 effect curve over 24.5 hours postdose for each period corrected for baseline value.
PF-03635659 doses 180, 580 and 1450 µg correspond to FPD 40, 128 and 320 µg, respectively.
ANOVA = analysis of variance; AUEC = area under the effect curve; CI = credible interval; FAS = full analysis set; FPD = fine particle doses; FEV1 = forced expiratory volume in 1 second; SE = standard error.

a. Excluding influential outliers. Any observation with a studentized residual greater than ±3 was considered as an influential outlier and therefore excluded from the analysis. There were no influential outliers.
b. Lower 1–sided 90% CI.

Table 11. Secondary Analysis: ANOVA Model - Change From Baseline in Weighted Average FEV_1 (Comparison of PF-03635659 to Tiotropium) - FAS[a]

Comparison	Estimate (L)	SE	CI[b]
PF-03635659 180 µg – Tiotropium 18 µg	-0.0674	0.0211	-0.0946
PF-03635659 580 µg – Tiotropium 18 µg	-0.0108	0.0213	-0.0383
PF-03635659 1450 µg – Tiotropium 18 µg	0.0166	0.0213	-0.0110

Weighted average FEV_1 response was defined as the AUEC change from baseline FEV_1, divided by 24.5 hours. AUEC was defined as the area under the FEV_1 effect curve over 24.5 hours postdose for each period corrected for baseline value.
PF-03635659 doses 180, 580 and 1450 µg correspond to FPD 40, 128 and 320 µg, respectively.
ANOVA = analysis of variance; AUEC = area under the effect curve; CI = credible interval; FAS = full analysis set; FPD = fine particle doses; FEV1 = forced expiratory volume in 1 second; SE = standard error.

a. Excluding influential outliers. Any observation with a studentized residual greater than ±3 was considered as an influential outlier and therefore excluded from the analysis. There were no influential outliers.
b. Lower 1–sided 90% CI.

Forced Vital Capacity and Inspiratory Capacity: FVC and IC data were summarized using descriptive statistics. The 3 dose levels of PF-03635659 and tiotropium 18 µg all showed clear effects on both FVC and IC compared to placebo. These effects appeared to be maintained for up to 48 hours postdose.

Safety Results:

An overview of treatment-emergent, all causality (treatment-related in parenthesis) AEs is presented in Table 12. Ten (10) of the 22 treated subjects experienced treatment-emergent AEs. A total of 2, 3, 1, 6 and 4 subjects reported AEs following PF-03635659 180, 580 and 1450 µg, tiotropium 18 µg and placebo, respectively.

Table 12. Overview of Treatment-Emergent Adverse Events - All Causality (Treatment-Related)

	PF-03635659 180 µg	PF-03635659 580 µg	PF-03635659 1450 µg	Tiotropium 18 µg	Placebo
Subjects evaluable for adverse events	22	22	21	22	22
Number of adverse events	2 (2)	3 (2)	1 (0)	7 (3)	4 (1)
Subjects with adverse events	2 (2)	3 (2)	1 (0)	6 (3)	4 (1)
Subjects with serious adverse events	0	0	0	1 (0)	0
Subjects with severe adverse events	0	0	0	0	0
Subjects discontinued due to adverse events	0	0	0	1 (1)	0
Subjects with dose reduced or temporary discontinuation due to adverse events	0	0	0	0	0

Subjects with treatment-related adverse events are presented in parentheses.

Table 13 summarizes the incidence of treatment-emergent all causality non-serious AEs. Headache was the only AE that occurred in >1 subject in any treatment group. This was

reported in 2 subjects each following 180 and 580 µg doses of PF-03635659 and tiotropium, and in 3 subjects following placebo.

Table 14 summarizes the incidence of treatment-emergent treatment-related AEs.

All doses of PF-03635659 were well tolerated and there were no deaths, treatment-related serious AEs (SAEs) or severe AEs reported. One subject, a 61-year old female, experienced a non treatment-related AE (pain in extremity) that started nearly 6 days after receiving tiotropium 18 µg. She was hospitalized with a suspicion of deep vein thrombosis, which was then confirmed not to be the case. This qualified as a SAE because of the hospital admission, but was not judged to be treatment-related by the Investigator. Table 15 summarizes the incidence of treatment-emergent SAEs.

One subject, a 58-year old male, discontinued from the study following tiotropium 18 µg due to mild treatment-related atrial flutter in Period 4. This was first recorded in just under 4 hours after receiving tiotropium 18 µg and was present on ECG recordings until 48 hours postdose. No other subjects were discontinued from the study due to AEs, nor did the reported AEs lead to any change in the planned dosing schedule.

Table 13. Treatment-Emergent Non-Serious Adverse Events by System Organ Class and Preferred Term - All Causalities

System Organ Class and Adverse Event Preferred Term (MedDRA)	PF-03635659 180 µg n (%)	PF-03635659 580 µg n (%)	PF-03635659 1450 µg n (%)	Tiotropium 18 µg n (%)	Placebo n (%)
Number (%) of subjects:					
Evaluable for adverse events	22	22	21	22	22
With adverse events	2 (9.1)	3 (13.6)	1 (4.8)	6 (27.3)	4 (18.2)
Cardiac disorders	0	0	0	1 (4.5)	0
Atrial flutter	0	0	0	1 (4.5)	0
General disorders and administration site conditions	0	1 (4.5)	0	1 (4.5)	0
Application site irritation	0	1 (4.5)	0	0	0
Chest pain	0	0	0	1 (4.5)	0
Musculoskeletal and connective tissue disorders	0	0	0	1 (4.5)	0
Musculoskeletal chest pain	0	0	0	1 (4.5)	0
Nervous system disorders	2 (9.1)	2 (9.1)	0	2 (9.1)	3 (13.6)
Headache	2 (9.1)	2 (9.1)	0	2 (9.1)	3 (13.6)
Respiratory, thoracic and mediastinal disorders	0	0	1 (4.8)	0	0
Epistaxis	0	0	1 (4.8)	0	0
Vascular disorder	0	0	0	1 (4.5)	1 (4.5)
Hematoma	0	0	0	1 (4.5)	1 (4.5)

Subjects were only counted once per treatment for each row.
Includes all data collected since the first dose of study drug.
MedDRA (version 13.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects.

Table 14. Incidence of Treatment-Emergent Adverse Events - Treatment-Related

System Organ Class and Adverse Event Preferred Term (MedDRA)	PF-03635659 180 µg (N=22)	PF-03635659 580 µg (N=22)	PF-03635659 1450 µg (N=21)	Tiotropium 18 µg (N=22)	Placebo (N=22)
Cardiac disorders	0	0	0	1	0
Atrial flutter	0	0	0	1	0
Nervous system disorders	2	2	0	2	1
Headache	2	2	0	2	1

Subjects were counted only once per treatment in each row.
Includes all data collected since the first dose of study drug.
MedDRA (version 13.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects.

Table 15. Incidence of Treatment-Emergent Serious Adverse Events - All Causalities

System Organ Class and Adverse Event Preferred Term (MedDRA)	PF-03635659 180 µg n (%)	PF-03635659 580 µg n (%)	PF-03635659 1450 µg n (%)	Tiotropium 18 µg n (%)	Placebo n (%)
Number (%) of subjects:					
Evaluable for adverse events	22	22	21	22	22
With adverse events	0	0	0	1 (4.5)	0
Musculoskeletal and connective tissue disorders	0	0	0	1 (4.5)	0
Pain in extremity	0	0	0	1 (4.5)	0

Subjects were counted only once per treatment in each row.
Includes all data collected since the first dose of study drug.
MedDRA (version 13.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects.

There were no laboratory abnormalities that were different from placebo, considered to be clinically significant or reported as AEs. BP, heart rate and ECG mean values did not show any treatment-related changes.

CONCLUSIONS:

- PF-03635659, delivered via the CRC749 inhaler device in moderate COPD subjects, demonstrated dose-response relationships on trough, peak and average FEV_1 relative to placebo. All doses studied (180, 580, 1450 μg: 40, 128, 320 μg FPDs) showed a high probability of superiority to placebo (as did the positive control tiotropium 18 μg).

- PF-03635659 systemic plasma exposure in COPD subjects was low following administration of single oral inhalation doses of PF-03635659 180, 580 and 1450 μg. PF-03635659 absorption was rapid with C_{max} generally occurring within the first hour after dosing. PF-03635659 exposure as measured by AUC_{last} and C_{max} increased with an increase in dose with greater than dose proportional (approximately 2-fold higher) increases in AUC_{last} values observed between the 580 and the 1450 μg doses and dose proportional increases in mean geometric C_{max} values across all dose groups.

- PF-03635659 doses 580 and 1450 μg had similar effects over placebo to the positive control tiotropium 18 μg for trough, peak and weighted average FEV_1.

- PF-03635659 was safe and very well tolerated when administered using the CRC749 device in single doses up to 1450 μg in COPD subjects.