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GENERIC DRUG NAME and/or COMPOUND NUMBER: PF-00610355

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: This drug is not marketed in the United States.

NATIONAL CLINICAL TRIAL NO.: NCT00808288

PROTOCOL NO.: A7881013

PROTOCOL TITLE: A Phase 2B, Parallel, Double Blind, Double Dummy, Active Comparator and Placebo Controlled Study to Investigate the Safety, Toleration and Efficacy of 6-Week QD Administration of PF-00610355 CRC-749 DPI in Patients with Moderate COPD

Study Center(s): 67 centers in 12 countries: United States (23), Argentina (3), Bulgaria (4), Croatia (2), Czech Republic (4), Germany (8), Hungary (5), Poland (4), Slovakia (6), South Africa (4), Spain (2), and Turkey (2)

Study Initiation Date and Primary Completion or Completion Dates: 15 March 2010 to 20 December 2010

Phase of Development: Phase 2B

Study Objective(s):

Primary

- To test all doses (100, 300, and 600 μg once daily [QD]) of PF-00610355 and salmeterol 50 μg twice daily (BID) for superior efficacy on trough forced expiratory volume in 1 second (FEV_1) vs placebo at Week 6.

Secondary

- To test all doses of PF-00610355 and salmeterol 50 μg for superior efficacy on peak FEV_1 vs placebo at Day 1 and Week 6.
- To characterise dose/response vs placebo at Week 6.
- To test all doses of PF-00610355 and salmeterol for superior efficacy on quality of life (QOL), chronic obstructive pulmonary disease (COPD) symptoms, and dyspnea and rescue medication use vs placebo.

- To test all doses and salmeterol for superior efficacy vs placebo at Weeks 2 and 4.

- To investigate the dose response relationship of PF-00610355 vs β2-mediated extra pulmonary effects in COPD patients, specifically: heart rate, blood pressure, QTc (QT interval corrected for heart rate), arrhythmias, and plasma potassium.

METHODS

Study Design: This was a parallel-design, randomized, double-blind, double-dummy, active-comparator, and placebo-controlled 5-arm study in the treatment of subjects with moderate COPD.

All subjects had a 3-week run-in period. Subjects using bronchodilators were permitted only salbutamol for the duration of the run-in and study period, and for subjects using inhalers combining inhaled corticosteroids and β2-agonists, the corticosteroid component was replaced with the equivalent inhaled corticosteroid inhaler. Subjects on inhaled corticosteroid monotherapy prior to run-in continued on their pre-study regimen.

Subjects were to be able to manage their symptoms adequately with salbutamol only, with a maximum of 8 actuations (100 μg/actuation) daily. Subjects were asked to abstain from salbutamol from 6 hours prior to the start of each visit.

Each subject visited the clinical unit on 8 occasions. To minimize variability in bronchomotor tone due to circadian changes, tests on each visit were to be performed at the same time of day.

Number of Subjects (Planned and Analyzed): Approximately 72 subjects per arm were to be randomized (~400 subjects were to be randomized to achieve approximately 360 completed subjects)**.** Of the 405 subjects who were randomized to treatment and received at least 1 dose of study medication, 81 were in the 100-μg group, 88 were in the 300-μg group, 81 were in the 600-μg group, 74 were in the placebo group, and 81 were in the salmeterol group.

Diagnosis and Main Criteria for Inclusion: Male or female subjects between, and including, the ages of 40 and 80 years with a diagnosis, for at least 6 months, of moderate COPD and who met the criteria for Stage II disease were enrolled in the study. Subjects must have had a smoking history of at least 10 pack-years and had stable disease for at least 1 month prior to screening. Subjects were not included in the study if they had more than 2 exacerbations of COPD requiring treatment with oral steroids in the preceding year or hospitalization for the treatment of COPD within 3 months of screening or more than twice during the preceding year.

Study Treatment: Subjects were randomized to one of the following 5 treatment groups: PF-00610355 100 μg, PF-00610355 300 μg, PF-00610355 600 μg, placebo, and salmeterol 50 μg.

Study drug was administered by inhalation for both CRC-749 dry powder inhaler (DPI) for PF-00610355 and matching placebo and Accuhaler™ (Diskus® for United States) for salmeterol and matching placebo. Subjects were instructed to take 1 puff once a day in the morning from CRC-749 DPI or matching placebo and 1 puff twice a day, once in the morning and once in the evening from Accuhaler™ or matching placebo. Subjects were thoroughly trained in the use of both devices and first administration was guided and supervised by study staff to ensure compliance.

Efficacy Evaluations: Spirometry (FEV_1 and forced vital capacity [FVC]) was performed at Visits 1 and 2 (both pre- and post-bronchodilator use) to assess/confirm eligibility. At Visit 3, spirometry was performed predose and at 1, 2, 3, 4, 6, and 24 hours postdose. At Visits 4 and 5, spirometry was performed predose only. At Visit 6, spirometry was performed predose and at 1, 2, 3, 4, and 6 hours postdose. At Visits 3 and 6, the predose tests were repeated as these were used to calculate the primary endpoint.

At selected sites, the Chronic Respiratory Questionnaire Self-Administered Standardized (CRQ-SAS) was completed at the beginning of the study visit, before the subject had any significant contact with study personnel. Specifically, the questionnaires were completed before collection of concomitant medication or adverse event (AE) data, and before the performance of any study-specific procedures.

Dyspnea was assessed during the study using the Baseline Dyspnea Index /Transition Dyspnea Index (BDI/TDI). The BDI was administered at Week 0; the TDI was administered at Weeks 2, 4, and 6. The BDI scored the magnitude of effort, types of tasks, both work and non-work, which make the subject breathless, as well as the level of functional impairment. The TDI measured changes from this baseline state.

Pharmacokinetic and Pharmacodynamic Evaluations: At selected sites, blood samples (5 mL) for measurements of plasma PF-00610355 concentration were collected at the following times and visits:

- Visit 3/Day 1/baseline: predose and at 1-2 hours, 5-6 hours, and 24 hours
- Visit 6/Week 6/end of study: predose and at 1-2 hours, and 5-6 hours

In addition to the potassium analysis provided within the safety laboratory assessments, additional samples were taken predose and at 1-2 and 3-4 hours postdose for the analysis of potassium at Visit 3 (Day 1) and Visit 6 (Week 6). Potassium measurements done 1-2 and 3-4 hours postdose were analyzed locally and reviewed within 24 hours of collection (before administering the second dose at Visit 3).

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

Statistical Methods:

The full analysis set (FAS) consisted of all subjects who had been randomized to study treatment, received at least 1 dose of study medication, and had at least 1 on-treatment efficacy evaluation (spirometry-based, questionnaire-based, or diary-based).

The per protocol analysis set (PPAS) consisted of all subjects who, in addition to the FAS criteria, satisfied the following criteria: completed 6 weeks of double-blind treatment, treatment compliance was greater than 80%, had valid baseline and Week 6 assessments, had not violated any inclusion or exclusion criteria that influenced the efficacy outcome (prior to randomization), and had not violated the protocol, or deviated from the protocol, in such a way that influenced the efficacy outcome (post randomization).

The safety analysis set (SS) consisted of all subjects randomized at Visit 3 (baseline) who received at least 1 dose of double-blind treatment.

The outliers removed analysis set (ORAS) excluded subjects from the FAS who had a change from baseline in trough FEV_1 outside the range ±700 mL at Week 2, 4, or 6. Subjects with missing data at Weeks 2, 4, or 6 were included.

The primary endpoint, trough FEV_1, was analyzed using a repeated measures mixed effects analysis of covariance (ANCOVA) model with baseline value, treatment, week, country, smoking status, and treatment by week as fixed effects terms. This model allowed the time course of response to treatment to be investigated. A compound symmetry covariance structure was applied.

Efficacy

The primary efficacy endpoint was the change from baseline trough FEV_1 at Week 6. The term "trough" was defined as the predose value and the term "peak" was defined as the largest postdose value (up to 6 hours). Baselines for trough FEV_1 were defined as the weighted mean of 3 measurements: the pre-bronchodilator value from Visit 2, and the 2 predose values from Visit 3.

There were 4 trough FEV_1 values per subject: baseline, Week 2, Week 4, and Week 6. All data were fitted to the repeated measures model and the Week 2, Week 4, and Week 6 treatment contrasts were generated from the treatment-by-week interaction term.

The primary subject population for the analysis of the primary endpoint was the FAS with missing values included.

In addition to the analysis, summary statistics (mean, standard deviation, minimum, maximum) were presented by treatment group. Box and whisker plots were also presented by treatment group. Tables of mean baseline and mean absolute and percentage change from baseline in FEV_1 were presented by treatment group.

The following secondary endpoints were analyzed in the same manner as the primary endpoint, using the repeated measures ANCOVA model:

- Change from baseline in peak (0-6 hours after administration of study drug) FEV_1 on Day 1 and at Week 6.
- Change from baseline in trough and peak FVC on Day 1 and at Week 6.
- Change from baseline in trough FEV_1 and FVC at 2 and 4 weeks of therapy.
- Change from baseline in CRQ-SAS and the BDI/TDI scores at 2, 4, and 6 weeks.
- Change from baseline of COPD symptoms and rescue bronchodilator use (per daily diary).

The change from baseline in rescue bronchodilator use was analyzed by calculating the mean number of puffs per day for each week (using visit windows to define study weeks). Mean number of puffs per day was tabulated by treatment group and week.

Pharmacokinetics

Plasma concentration data for PF-00610355 were listed and summarized by treatment group, week, and time postdose. A population analysis of time versus plasma concentration data of PF-00610355 was performed using the non-linear mixed effect modeling approach. The effects of covariates on the models were explored, and those that improved the goodness of fit were included in the models.

Safety

Adverse events, laboratory safety test results, and ECG results were summarized using the sponsor's data standards. The safety population consisted of all subjects who received at least 1 dose of study drug (ie, subjects in the SS).

RESULTS

Subject Disposition and Demography: Overall, 883 subjects were screened for the study (Table 1); 405 were randomized to treatment and received at least 1 dose of study medication. A total of 28 subjects discontinued the study.

Table 1. Subject Evaluation Groups

	PF-00610355				Salmeterol
	100 µg QD	300 µg QD	600 µg QD	Placebo	50 µg BID
Screened 883					
Assigned to Study Treatment	81	88	81	74	81
Treated	81	88	81	74	81
Completed	76 (93.8)	83 (94.3)	71 (87.7)	71 (95.9)	76 (93.8)
Discontinued	5 (6.2)	5 (5.7)	10 (12.3)	3 (4.1)	5 (6.2)
Analyzed for Efficacy:					
Full Analysis Set	81 (100.0)	88 (100.0)	81 (100.0)	74 (100.0)	81 (100.0)
Per Protocol Analysis Set	68 (84.0)	75 (85.2)	68 (84.0)	67 (90.5)	70 (86.4)
Outliers Removed Analysis Set	81 (100.0)	86 (97.7)	81 (100.0)	71 (95.9)	81 (100.0)
Complete Case Analysis Set	78 (96.3)	86 (97.7)	79 (97.5)	74 (100.0)	81 (100.0)
Analyzed for Safety:					
Adverse events	81 (100.0)	88 (100.0)	80 (98.8)	74 (100.0)	81 (100.0)
Laboratory data	79 (97.5)	88 (100.0)	81 (100.0)	74 (100.0)	81 (100.0)
Safety Analysis Set	81 (100.0)	88 (100.0)	81 (100.0)	74 (100.0)	81 (100.0)

Discontinuations occurring outside the lag period were attributed to the study treatment received.
Abbreviations: BID = twice daily, QD = once daily.

Table 2 presents a summary of the demographic characteristics for the overall population. Overall, 63.5% of subjects were male. The mean age ranged from 61.4 years in the 300-µg group to 62.4 years in the placebo group. Most subjects (93.8%) were white. The demographic characteristics among the groups were generally similar.

Table 2. Demographic Characteristics

	PF-00610355				Salmeterol
	100 µg QD	300 µg QD	600 µg QD	Placebo	50 µg BID
No. of Subjects	81	88	81	74	81
Gender					
Male	58	62	45	42	50
Female	23	26	36	32	31
Age (years)					
Mean	61.6	61.4	62.2	62.4	62.0
Standard Deviation	8.9	8.2	8.3	8.9	8.2
Range	42-78	43-80	43-79	42-79	45-78
Race					
White	77 (95.1)	84 (95.5)	75 (92.6)	69 (93.2)	75 (92.6)
Black	1 (1.2)	2 (2.3)	4 (4.9)	3 (4.1)	3 (3.7)
Other	3 (3.7)	2 (2.3)	2 (2.5)	2 (2.7)	3 (3.7)

Abbreviations: BID = twice daily, QD = once daily.

Efficacy Results: A summary of the changes from baseline at Weeks 2, 4, and 6 in trough FEV_1 is presented in Table 3 for the FAS. At Week 6, the observed mean change from baseline in trough FEV_1 was 0.0610 L for the 100-µg group, 0.0685 L for the 300-µg group, 0.1116 L for the 600-µg group, -0.0617 L for the placebo group, and 0.0661 L for the salmeterol group. At each week of treatment, the difference between the PF-00610355 and

placebo groups was statistically significant ($p \leq 0.001$) and clinically meaningful (greater than the minimum clinically important difference of 0.1 L).

Table 3. Summary of Changes From Baseline in Trough FEV_1 (L) by Visit: FAS

	PF-00610355				
	100 µg QD	300 µg QD	600 µg QD	Placebo	Salmeterol 50 µg BID
Day 1 (Baseline)					
n	80	88	81	73	81
Mean	1.7460	1.6577	1.5786	1.5938	1.6130
Standard Deviation	0.53289	0.45244	0.39789	0.45231	0.47839
Median	1.7320	1.6178	1.6220	1.5450	1.5335
Minimum	0.769	0.788	0.636	0.805	0.746
Maximum	3.314	2.743	2.411	2.954	2.935
Week 2					
n	75	86	75	73	78
Mean Change From Baseline	0.0547	0.0899	0.1399	-0.0481	0.0386
Standard Deviation	0.18965	0.18600	0.17953	0.18712	0.16842
Median Change From Baseline	0.0680	0.1030	0.1595	-0.0375	0.0309
Minimum	-0.463	-0.404	-0.402	-0.806	-0.393
Maximum	0.437	0.647	0.475	0.721	0.506
Week 4					
n	76	85	74	72	78
Mean Change From Baseline	0.0432	0.0801	0.1133	-0.0811	0.0263
Standard Deviation	0.21788	0.22258	0.18938	0.19774	0.18834
Median Change From Baseline	0.0299	0.0617	0.1466	-0.0597	0.0399
Minimum	-0.545	-0.653	-0.494	-0.679	-0.646
Maximum	0.616	0.624	0.487	0.498	0.439
Week 6					
n	78	86	79	74	81
Mean Change From Baseline	0.0610	0.0685	0.1116	-0.0617	0.0661
Standard Deviation	0.17864	0.23295	0.18965	0.17177	0.16686
Median Change From Baseline	0.0417	0.0746	0.1150	-0.0486	0.0758
Minimum	-0.384	-0.795	-0.466	-0.802	-0.362
Maximum	0.534	0.961	0.524	0.273	0.553

Baseline is the weighted mean of the pre-bronchodilator value from the Week -1 visit and the 2 predose values from Day 1.
Abbreviations: FEV_1 = forced expiratory volume in 1 second; FAS = full analysis set; BID = twice daily, QD = once daily.

In general, the results of the changes from baseline at Weeks 2, 4, and 6 in trough FEV_1 for the ORAS and PPAS were similar to that for the FAS.

Peak FEV_1

At Week 6, the observed mean change from baseline in peak FEV_1 was 0.1831 L for the 100-µg group, 0.1542 L for the 300-µg group, 0.1210 L for the 600-µg group, 0.1307 L for the placebo group, and 0.1492 L for the salmeterol group. The difference between the 100-µg and placebo groups was statistically significant (0.0560 L, p = 0.0095).

Peak and Trough FVC

At Week 6, the observed mean change from baseline in trough FVC was 0.0374 L for the 100-µg group, 0.0968 L for the 300-µg group, 0.1467 L for the 600-µg group, -0.1259 L for the placebo group, and 0.0594 L for the salmeterol group. The difference between the PF-00610355 and placebo groups was statistically significant ($p \leq 0.0006$).

At Week 6, the observed mean change from baseline in peak FVC was 0.2582 L for the 100-µg group, 0.2102 L for the 300-µg group, 0.1927 L for the 600-µg group, 0.2141 L for the placebo group, and 0.2368 L for the salmeterol group. There were no statistically significant differences between the PF-00610355 and placebo groups.

Rescue Medication

At each week of treatment, all treatment groups had a mean decrease in the use of bronchodilator rescue medication. At Week 6, the mean change from baseline was -1.34 puffs/day for the 100-µg group, -1.17 puffs/day for the 300-µg group, -1.49 puffs/day for the 600-µg group, -0.43 puffs/day for the placebo group, and -1.23 puffs/day for the salmeterol group. The difference between the PF-00610355 and placebo groups was statistically significant ($p \leq 0.0072$).

CRQ-SAS

For each domain score of the CRQ-SAS, the PF-00610355 treatment groups had larger mean increases from baseline compared to the mean increase for the placebo group. The differences between the PF-00610355 and placebo groups were statistically significant ($p \leq 0.0442$) for the 100-µg and 300-µg groups for the dyspnea domain, and for the 100-µg group for the mastery domain.

BDI/TDI

For the 3 domains of the TDI (Functional Impairment, Magnitude of Task, and Magnitude of Effect) and the total score, the differences between the PF-00610355 and placebo groups were statistically significant ($p < 0.05$) for the 100-µg and 600-µg groups for all 4 domains of the TDI. The difference between the PF-00610355 300-µg group and placebo group was statistically significant ($p = 0.0491$) only for the magnitude of effect domain of the TDI.

Pharmacokinetic Results: For all 3 PF-00610355 treatment groups, the highest median concentrations on Day 1 and Week 6 were observed at Hour 2.

Safety Results: Table 4 presents a summary of treatment-emergent adverse evens (TEAEs) by all causality. Overall, 29 (35.8%) subjects reported 41 TEAEs in the 100-µg group, 37 (42.0%) subjects reported 52 TEAEs in the 300-µg group, 27 (33.3%) subjects reported 55 TEAEs in the 600-µg group, 21 (28.4%) subjects reported 41 TEAEs in the placebo group, and 23 (28.4%) subjects reported 33 TEAEs in the salmeterol group.

The incidence of severe AEs, serious adverse events (SAEs), and discontinuations due to AEs was slightly higher in the 100-µg and 600-µg groups (about 3 to 6 subjects for each category) compared to the 300-µg, placebo, and salmeterol groups (about 1 to 3 subjects each category). One subject in the 100-µg group had a dose reduction or temporary discontinuation due to an AE.

Table 4. Treatment-Emergent Adverse Events (All Causalities)

	PF-00610355								Salmeterol	
Number (%) of subjects:	**100 µg QD**		**300 µg QD**		**600 µg QD**		**Placebo**		**50 µg BID**	
Subjects evaluable for AEs	81		88		81		74		81	
Number of AEs	41		52		55		41		33	
Subjects with AEs	29	(35.8)	37	(42.0)	27	(33.3)	21	(28.4)	23	(28.4)
Subjects with serious AEs	4	(4.9)	1	(1.1)	3	(3.7)	2	(2.7)	1	(1.2)
Subjects with severe AEs	5	(6.2)	1	(1.1)	3	(3.7)	1	(1.4)	2	(2.5)
Subjects discontinued due to AEs	4	(4.9)	2	(2.3)	6	(7.4)	1	(1.4)	3	(3.7)
Subjects with dose reduced or temporary discontinuation due to AEs	1	(1.2)	0		0		0		0	

Includes data up to 28 days after last dose of study drug.
Except for the number of AEs subjects are counted only once per treatment in each row.
Serious adverse events - according to the investigator's assessment.
MedDRA (v13.1) coding dictionary applied.
Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; AEs = adverse events; BID = twice daily, QD = once daily.

The most common AEs were exacerbation of COPD (reported by 3 [3.7%] subjects in the 100-µg group, 1 [1.1%] subject in the 300-µg group, 5 [6.2%] subjects in the 600-µg group, 2 [2.7%] subjects in the placebo group, and 1 [1.2%] subject in the salmeterol group) and nasopharyngitis (reported by 5 [6.2%] subjects in the 100-µg group, 2 [2.3%] subjects in the 300-µg group, 1 [1.2%] subject in the 600-µg group, 4 [5.4%] subjects in the placebo group, and no subjects in the salmeterol group).

Overall, 7 (8.6%) subjects reported 9 treatment-related TEAEs in the 100-µg group, 14 (15.9%) subjects reported 17 treatment-related TEAEs in the 300-µg group, 9 (11.1%) subjects reported 13 treatment-related TEAEs in the 600-µg group, 8 (10.8%) subjects reported 10 treatment-related TEAEs in the placebo group, and 2 (2.5%) subjects reported 2 treatment-related TEAEs in the salmeterol group.

Treatment-related TEAEs by preferred term were reported by 1 subject per treatment group, except for dry mouth, reported by 3 (3.4%) subjects in the 300-µg group; ECG T wave inversion, reported by 2 (2.3%) subjects in the 300-µg group; and muscle spasms, reported by 2 (2.5%) subjects in the 600-µg group.

One subject died during the study. A 58-year-old white female in the salmeterol group died on Day 45 of the study due to heart failure. The investigator did not consider the event related to study medication.

A total of 11 subjects reported SAEs during the study. Of these, 1 (atrial fibrillation in the 600-µg group) was considered to be related to PF-00610355 treatment.

Sixteen subjects discontinued the study due to an AE, of which 5 (2 in the 100-µg group, 1 in the 300-µg group, and 2 in the 600-µg group) were considered to be related to PF-00610355 treatment. Three subjects in 600-µg group and 1 in the placebo group discontinued due to exacerbation of COPD.

For laboratory evaluations, the median changes, in general, were small and not clinically significant. The median changes were generally similar among the treatment groups. The incidence of laboratory test abnormalities was generally similar among the treatment groups. Most of the abnormalities were observed for hematology parameters.

For potassium, the median change from baseline and mean maximum change from baseline was similar among the 5 treatment groups. Only 1 subject (100-µg group) had an abnormal potassium value during the study.

Overall, the mean changes in systolic and diastolic blood pressure were small and not clinically meaningful. For heart rate, the mean change was similar among the treatment groups (range: -1.6 beats per minute [bpm] to 0.8 bpm), except for the 600-µg group, which had an increase of 3.9 bpm. In general, the mean maximum change for systolic and diastolic blood pressure and pulse rate were similar among the 5 treatment groups.

Overall, the mean changes in ECG results were small and not clinically meaningful. In general, the mean maximum change for ECG results was similar among the 5 treatment groups. No subject in the PF-00610355 groups had a QT interval ≥500 msec or a QTcF (QT interval corrected for heart rate using Fridericia's formula) interval >480 msec. A similar percentage of subjects in all treatment groups (6.9% to 12.3%) had an increase from baseline in QTcF interval between 30 msec and 60 msec. An increase from baseline in QTcF interval ≥60 msec was reported by 2 (2.3%) subjects in the 300-µg group and 1 (1.2%) subject in the 600-µg group.

CONCLUSION(S): The efficacy results demonstrate that changes from baseline in trough FEV_1 at Week 6 for all PF-00610355 doses were superior to placebo ($p<0.0001$). The changes were clinically meaningful. Sensitivity analysis confirmed the scientific integrity of the study and robustness of primary endpoint interpretation. All PF-00610355 doses were well tolerated and the incidences of AEs were low. The type of AEs observed during the study was representative for the class.