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COMPOUND NUMBER: PF-610,355

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS:

NCT NO.: N/A

PROTOCOL NO.: A7881004

PROTOCOL TITLE: A Phase IIa Randomised, Double-Blind, Double-Dummy, Placebo and Active Controlled 5-Way Cross-Over Trial to Examine the Bronchodilator Effects of PF-610,355 and to Test for Superiority Versus Placebo in Reversible Asthmatic Patients

Study Centers: Germany – 3 centers, Sweden – 2 centers, UK – 1 center.

Study Initiation and Completion Dates: 06 July 2007 to 09 November 2007

Phase of Development: Phase 2a

Study Objectives:

Primary Objectives

- To test all doses of PF-610,355 for superiority of trough (24 hour post-dose) forced expiratory volume in 1 second (FEV_1) versus placebo.
- To characterize the relationship of PF-610,355 dose to peak and trough FEV_1.

Secondary Objectives

- To characterize the relationship of PF-610,355 dose to peak and trough peak expiratory flow rate (PEFR).
- To test all doses of PF-610,355 for superiority of trough (24 hour post-dose) PEFR versus placebo.
- To 'bench-mark' the efficacy (FEV_1 peak effect) of PF-610,355 against salmeterol 50 μg.
- To investigate the pharmacokinetics (PK) of PF-610,355 delivered via CRC749 in asthmatic subjects.
- To investigate the safety and toleration of PF-610,355 delivered via CRC749 in asthmatic subjects.

Exploratory Objective

- Using a model-based approach, to describe the PF-610,355 dose-FEV_1 response profile over time.

METHODS

Study Design: This was a randomized, double-blind, double-dummy, placebo and active controlled, 5-way partially balanced incomplete block crossover study in adult subjects with persistent asthma.

Since asthma is equally prevalent in both sexes and PF-610,355 did not cause any adverse effects in embryo-fetal development studies, both males and females were recruited.
The study comprised of 8 clinical visits: Screening 1 (Visit 1) within 28 days of the first dosing day; Screening 2 (Visit 2); 5 treatment periods (Visits 3 to 7); and a follow-up visit 10 to 14 days post final dose (Visit 8). Subjects were dosed on the first day of each treatment period.

Subjects qualifying to enter the double-blind treatment periods were to be randomized at Period 1 (Visit 3) to 1 of 30 discrete sequences of treatment administration, so that over the 5 treatment periods each subject received 5 of the 6 treatments studied.

The 6 treatments were:

- Double-blind placebo.
- PF-610,355 (108 μg) + placebo (for salmeterol).
- PF-610,355 (368 μg) + placebo (for salmeterol).
- PF-610,355 (736 μg) + placebo (for salmeterol).
- PF-610,355 (1472 μg) + placebo (for salmeterol).
- Placebo (for PF-610,355) + salmeterol (50 μg).

There was a minimum of 7 days between each treatment period. Study duration (randomization to final dose) was ideally to be within a 7-week period.

Number of Subjects (Planned and Analyzed): It was planned to randomize approximately 42 subjects. The actual number of subjects randomized was 43.

Diagnosis and Main Criteria for Inclusion: Male and female subjects aged 18 to 65 years inclusive with a physician documented history or diagnosis of persistent, reversible asthma (according to the Global Initiative in Asthma, 2006 definition of asthma) for at least 6 months prior to Screening 1 (Visit 1) were eligible for entry to this study. Subjects also had to have a Screening 1 (Visit 1) FEV_1 measure of >60% of predicted value for age, height, and sex (using European Community for Coal and Steel standards) following withdrawal of long acting β2-adrenoreceptor agonist (LABA) for a minimum of 72 hours and short acting β2-adrenoreceptor agonist (SABA) for a minimum of 8 hours, and had to demonstrate ≥15% improvement in FEV_1 (and ≥200 mL increase) within 15 to 45 minutes following 200 μg salbutamol administration.

Study Treatment: The PF-610,355/placebo CRC749 Multi-dose Dry Powder Inhalers were supplied by the sponsor. The strengths supplied were 54 and 184 μg. Salmeterol was supplied as Serevent® (salmeterol xinafoate) 25 μg/metered dose inhaler (MDI) by the sponsor. Two puffs of the inhaler provided the nominal 50 μg dose. For both treatments, matching placebo was supplied to allow double-dummy blinding. Salbutamol (MDIs) for use as rescue medication was sourced locally. Salbutamol (MDIs) was also supplied to determine reversibility of subjects at screening and was used with a spacer. Two puffs provided the 200 μg nominal dose.

On each dosing occasion, dosing with study treatment took place before 8 am. For an individual subject, dosing on each of the 5 periods took place within ±1 hour of the dosing time on Period 1 to minimize the effect of diurnal variation. There was a minimum of 7 days between each treatment period.

Inhaled corticosteroid (ICS) was taken prior to the start of study procedures between 2 hours and 1 hour before dosing with study treatment. For those on twice daily ICS treatment, subjects took the evening dose 12 (±2) hours after the morning dose.

Efficacy Evaluations: FEV_1 was the primary efficacy measure. PEFR was the secondary efficacy lung function measure. FEV_1 and PEFR were measured at Periods 1 to 5 at the following timepoints: predose and at 15 and 30 minutes and 1, 2, 3, 4, 8, 12, 14, 16, 19, 22, 24, 26, 28, 30, and 32 hours post-dose.

Pharmacokinetic Evaluations: Blood samples (5 mL) to provide a minimum of 2 mL plasma for PK analysis of PF-610,355 concentration were collected pre-dose and at 2, 4, 8, 12, 19, and 24 hours post-dose on Periods 1 to 5. Blood samples (5 mL) to provide a minimum of 2 mL plasma for PK analysis of salmeterol concentration were collected pre-dose and at 5, 15, and 45 minutes post-dose on Periods 1 to 5.

The following PK parameters were to be summarized by dose for PF-610,355:
the maximum observed plasma concentration (C_{max}); the first time at which C_{max} was observed (T_{max}); the area under the plasma concentration-time curve (AUC); the AUC from time zero to the final sampling time (AUC_t); the AUC with dose normalized (AUC_{DN}) to 15 μg; and the terminal elimination half-life ($t_{1/2}$).

The following PK parameters were actually summarized by dose for PF-610,355:
C_{max}; T_{max}; the AUC from time zero to the last measurable concentration (AUC_{last}); the time at which AUC_{last} occurred (T_{last}); and $AUC_{t(DN)}$ to 1 μg.

Pharmacodynamic Evaluations: The pharmacodynamic variables, maximum increase and decrease (0 to 24 hours) from baseline for pulse rate, QTcF, and systolic and diastolic blood pressure, and maximum increase and decrease (0 to 12 hours) from baseline for plasma potassium were derived. These measurements were listed and summarized (n, mean, standard deviation, minimum and maximum) by treatment group. Box and whisker plots were presented by treatment group for maximum increase in pulse rate, QTcF, and systolic blood pressure, and maximum decrease in diastolic blood pressure and potassium.

Other Evaluations: This study also included the collection of a single blood sample for pharmacogenomic studies to examine the genetic basis of drug response (where appropriate) and to examine the genetic basis of asthma. Participation in this component of the study was voluntary.

Safety Evaluations: Safety evaluations included adverse events (AEs), vital signs (pulse rate and blood pressure), electrocardiograms (ECGs), physical examination, and safety laboratory tests.

Vital signs were measured at Screening; predose, and at 45 minutes and 3, 5, 8, and 24 hours post-dose in Periods 1 to 5; at discharge; and at Follow-up.

Single ECG measurements were performed at Screening, discharge (Periods 1 to 5), and Follow-up. Triplicate ECGs (approximately 2 to 4 minutes apart) were obtained in Periods 1 to 5 at the following timepoints: predose, and at 45 minutes, 3, 5, 8, and 24 hours post-dose.

A full physical examination was conducted at Screening and Follow-up, with a brief physical examination conducted prior to discharge in Periods 1 to 5.

Blood samples were collected for safety laboratory tests at Screening; predose in Periods 1 to 5; prior to discharge; and at Follow-up.

Statistical Methods: The primary analyses included trough and peak FEV_1; the secondary analyses included trough and peak PEFR; and the exploratory analyses included FEV_1 $AUEC_{[0-32]}$, time to onset of action of FEV_1, time to offset of action of FEV_1, time to peak response of FEV_1.

The primary analysis was based on the Full Analysis Set (FAS). The Analysis of variance (ANOVA) model was used for the change from baseline in trough FEV_1. The EMAX model was used for analysis of the dose-response relationship versus peak and trough FEV_1. Missing values were not imputed. A sensitivity analysis of the primary endpoints was conducted to examine the robustness of the primary results. This analysis excluded subject data from periods where rescue medication was given (Efficacy Analysis Set [EAS]).

A mixed effects ANOVA was used with sequence, period, treatment group, and baseline spirometry considered fixed effects and subject within sequence considered a random effect. First-order carryover of treatment was also explored. Estimate of the adjusted mean differences between each of the 4 doses of PF-610,355 and placebo, associated standard errors and 95% 2-sided confidence intervals (CIs) were presented simultaneously. Dunnett's multiple comparisons test was used to control for multiplicity.

The comparisons of interest were:

PF-610,355 108 µg – Placebo
PF-610,355 368 µg – Placebo
PF-610,355 736 µg – Placebo
PF-610,355 1472 µg – Placebo

This analysis was performed as planned on the FAS. For the co-primary endpoint, change from baseline in trough FEV_1, and for the secondary endpoint, change from baseline in trough PEFR, a sensitivity analysis was also performed on the FAS excluding influential outliers, and on the EAS, which excluded subjects receiving rescue medication. For the exploratory endpoint FEV_1 $AUEC_{[0-32]}$, the analysis was performed on the FAS and the FAS excluding outliers.

An EMAX model was used to model the PF-610,355 data and placebo, to assess the dose response characteristics of PF-610,355 on change from baseline for trough and peak FEV_1 and trough and peak PEFR using PROC NLMIXED, SAS v8. This analysis was performed on the FAS and the EAS. A random term was used to describe the between subject variability. The salmeterol effect was modelled assuming a mean salmeterol effect plus a random between subjects effect.

Estimations of the difference between each dose of PF-610,355 and salmeterol, together with associated 90% CIs, were derived from this single model.

Originally, for time to onset data, the Hodges-Lehmann method was adopted, however, it was realised posthoc that this analysis was unsuitable as the assumptions of complete data were violated due to the unbalanced nature of the design. The proposed non-parametric analyses were replaced by parametric analyses. Time to peak effect and natural log transformed 'time to onset' and 'time to offset' were analyzed using a mixed ANOVA model, with period and treatment considered fixed effects and subject considered a random effect. This analysis was performed on the FAS. Treatment comparisons of PF-610,355 doses against placebo, and separately, PF-610,355 doses against salmeterol, were presented, together with 95% CIs.

RESULTS

Subject Disposition and Demography: Forty-three subjects were assigned to study treatment. Two subjects discontinued the study: 1 subject was withdrawn due to an AE and 1 subject was withdrawn as sufficient blood samples could not be obtained.

Table S1. Subject Disposition and Data Sets Analyzed

			PF-610,355				Salmeterol
		Placebo	108	368	736	1472	(50 µg)
Screened	97						
Assigned to study treatment	43						
Treated		34	35	36	36	34	35
Completed		34	35	36	36	33	34
Discontinued		0	0	0	0	1	1
Related to study drug		0	0	0	0	1	0
Adverse event		0	0	0	0	1	0
Analyzed for efficacy							
FAS – overall		34	35	36	36	34	35
FAS – trough FEV_1		33	35	36	36	33	35
FAS – peak FEV_1		34	35	36	36	34	35
FAS – trough PEFR		33	35	36	36	33	35
FAS – peak PEFR		34	35	36	36	34	35
EAS - overall		34	34	36	34	33	35
EAS – trough FEV_1		33	34	36	34	32	35
EAS – peak FEV_1		34	34	36	34	33	35
EAS – trough PEFR		33	34	36	34	32	35
EAS – peak PEFR		34	34	36	34	33	35
Analyzed for safety							
Adverse events		34	35	36	36	34	35
Laboratory data		33	35	36	36	33	35
Safety population		34	35	36	36	34	35

FAS: Full analysis set. EAS: Efficacy analysis set. FEV_1: Forced expiratory volume in 1 second. PEFR: Peak expiratory flow rate.

Approximately 2 thirds of the subjects were male and 1 third were female. The mean (SD) age was 39.7 (12.7) years. The majority of subjects were white. The mean (SD) body mass index for subjects was 26.5 (3.6) kg/m^2. The mean duration since first diagnosis with asthma was 23.6 years (range 6.0 to 52.0 years).

The mean (SD) pre-bronchodilator FEV_1 and % predicted FEV_1 for all subjects was 2.820 (0.587) L and 76.5 (9.5)%, respectively. The mean (SD) post-bronchodilator FEV_1 and % predicted FEV_1 was 3.413 (0.668) L and 92.8 (11.3)%, respectively. The mean (SD) % reversibility FEV_1 for all subjects was 21.5 (5.8)%. There were no notable differences between treatments in any of these baseline lung function measurements.

Efficacy Results:

Primary Evaluations

There was a greater mean change from baseline in trough FEV_1 for all doses of PF-610,355 compared with placebo. The 3 highest PF-610,355 doses (368, 736, and 1472 μg) were statistically superior to placebo with the ANOVA model.

There was a clear dose-response relationship for trough FEV_1 with adjusted mean change from baseline increasing with increasing dose of PF-610,355 with the ANOVA and EMAX models.

All doses of PF-610,355 resulted in a higher peak FEV_1 compared with placebo. Compared with salmeterol, all doses of PF-610,355 (with the exception of the 108 μg dose) resulted in a higher peak FEV_1.

There was a clear dose-response relationship for peak FEV_1 with a greater peak FEV_1 occurring with increasing dose of PF-610,355. The peak effect estimate of salmeterol was comparable to 368 and 736 μg PF-610,355 (EMAX model).

Secondary Evaluations

There was a greater change from baseline in trough and peak PEFR for all doses of PF-610,355 compared with placebo. For trough PEFR, the 3 highest PF-610,355 doses (368, 736, and 1472 μg) were statistically superior to placebo with the ANOVA model.

The dose-response relationship for peak PEFR was not as clear as the dose-response relationship for trough PEFR; however, the peak effect estimate of salmeterol was comparable to 736 μg PF-610,355 (EMAX model).

Exploratory Evaluations

There was a clear dose-response relationship with mean FEV_1 $AUEC_{0\text{-}32}$ increasing with increasing dose of PF-610,355. All doses of PF-610,355 were statistically superior to placebo using the ANOVA model.

Time to peak FEV_1 did not differ notably between treatments.

The time to onset of action of FEV_1 was shorter with increasing dose of PF-610,355.

The time to offset of action of FEV_1 was longer with increasing dose of PF-610,355 up to 736 μg PF-610,355 and was similar for 736 μg and 1472 μg PF-610,355 using the ANOVA model, however, data were truncated at 32 hours post-dose (the final sampling timepoint).

Pharmacokinetic Results: Plasma AUC_{last} and C_{max} increased in line with increasing dose and $AUC_{t\ (DN)}$ was similar for all doses.

Pharmacodynamic Results: Effects on systemic PD measurements, pulse rate, systolic and diastolic blood pressure, plasma potassium and QTcF were generally small and not distinguishable from placebo. However, there was a small dose-response trend for mean maximum decrease from baseline in plasma potassium (0-12 hours), and mean maximum increase from baseline in QTcF (0-24 hours).

Mean maximum decrease (0-12 hours) from baseline for plasma potassium increased with increasing dose of PF-610,355, with greater mean maximum decreases for 368, 736 and 1472 µg PF-610,355 compared with placebo and for 1472 µg PF-610,355 compared with salmeterol. The mean maximum decrease in plasma potassium for 368 and 736 µg PF-610,355 was similar to salmeterol. Five subjects reported AEs of hypokalaemia or blood potassium decreased within 12 hours of dosing.

Mean maximum increase from baseline for QTcF increased with increasing dose of PF-610,355. There was a greater mean maximum increase with all doses of PF-610,355 compared with placebo and with 368, 736, and 1472 µg PF-610,355 compared with salmeterol. The maximum recorded increase from baseline for QTcF increased with increasing dose of PF-610,355 and were all higher than the maximum recorded increase from baseline for placebo and salmeterol. The interquartile range was similar across doses, however, outliers were observed at the upper end of the normal distribution for each of the PF-610,355 doses. Four subjects reported ECG-related AEs within 24 hours after dosing with PF-610,355.

Safety Results: There were no deaths during this study. One SAE of suicidal ideation, which was not considered to be treatment-related, was reported in 1 subject after dosing with placebo. One subject was permanently discontinued after dosing with 1472 µg PF-610,355 due to a severe AE of AST increased that was considered to be treatment-related. This subject also had coincident small increases in QTcB. One subject had study drug stopped temporarily after dosing with salmeterol due to a severe AE of syncope, which was not considered to be treatment-related. A total of 111 all causality AEs was reported, 45 of these AEs were considered to be treatment-related. A notably greater number of treatment-related AEs were reported after dosing with 1472 µg PF-610, 355 compared with the other treatments. However, the number of subjects who experienced treatment-related AEs was similar for all treatments, including placebo and salmeterol.

The most commonly reported AE (all causalities and treatment-related) was headache.

Treatment-emergent all causality AEs by preferred term and treatment, that occurred in 2 or more subjects per treatment received are presented in Table S2.

Table S2. Summary of Treatment Emergent Adverse Events (All Causalities)

	Placebo (N=34)	PF-610,355 (µg) 108 (N=35)	368 (N=36)	736 (N=36)	1472 (N=34)	Salmeterol 50 µg (N=35)
	n	n	n	n	n	n
Nausea	0	1[a]	1[a]	0	0	2 (1[a])
Nasopharyngitis	2	3	0	1	1	0
ECG QT prolonged	0	0	1[a]	2[a]	2[a]	0
Hypokalaemia	1[a]	1[a]	1[a]	0	2[a]	2[a]
Headache	10 (3[a])	5 (2[a])	7 (3[a])	6 (2[a])	3 (1[a])	5 (1[a])
Tremor	0	0	0	2[a]	2[a]	0
Pharyngolaryngeal pain	0	2	0	1	2 (1[a])	0

N: Number of subjects evaluable for adverse events; n: Number of subjects; ECG: Electrocardiogram.
If the same subject in a given treatment had more than one occurrence in the same preferred term event category, only the most severe occurrence was taken. Subjects were counted only once per treatment in each row. For the TESS algorithm any missing severities were to be imputed as severe unless the subject experienced another occurrence of the same event in a given treatment for which severity was recorded. In this case, the reported severity was to be summarized. Missing baseline severities were imputed as mild. Includes data up to 14 days after last dose of study drug.
[a] Treatment-related adverse events.

There were increases in the incidence of treatment-related ECG QT prolonged and tremor with increasing dose of PF-610,355.

Five subjects reported 9 severe AEs during the study, of which, the AEs of headache, AST increased and transaminase increased were considered to be treatment-related.

Two AEs (suicidal ideation [SAE] and mild arthralgia) were ongoing at the end of the study.

CONCLUSIONS:

- The 3 highest PF-610,355 doses (368, 736, and 1472 µg) showed statistically significant superiority for trough FEV_1 versus placebo (ANOVA).
- There was a clear EMAX dose-response relationship for trough and peak FEV_1 with adjusted mean changes from baseline for both parameters increasing with increasing dose of PF-610,355.
- There was a clear dose-response relationship with adjusted mean change from baseline in trough PEFR increasing with increasing dose of PF-610,355. Adjusted mean change from baseline in peak PEFR also increased with increasing dose of PF-610,355, however, the dose-response relationship was not as clear as for trough PEFR.
- The 3 highest PF-610,355 doses (368, 736, and 1472 µg) showed statistically significant superiority for trough PEFR versus placebo (ANOVA).

- The efficacy (FEV_1 peak effect) of 50 µg salmeterol was comparable to 368 and 736 µg PF-610,355.

- Plasma AUC_{last} and C_{max} increased in line with increasing dose and $AUC_{t\ (DN)}$ was similar for all doses.

- All tested doses of PF-610,355, delivered via CRC749 in asthmatic subjects, were considered safe and well tolerated.