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**COMPOUND NUMBER:** PH-797804

**THERAPEUTIC AREA AND FDA APPROVED INDICATIONS:** Not applicable

**NATIONAL CLINICAL TRIAL NO.:** NCT00559910

**PROTOCOL NO.**: A6631011

**PROTOCOL TITLE**: A Phase 2, Randomized, Double Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Once-Daily Orally Administered PH-797804 (0.5, 3, 6 and 10 mg) in Adults with Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD)

**Study Centers:** Subjects were recruited at 38 study sites in 13 countries: Argentina (5), Australia (4), Canada (4), Chile (3), Czech Republic (5), France (2), Greece (1), Hungary (4), Republic of Korea (1), Netherlands (2), Russian Federation (3), South Africa (3), United Kingdom (1)

**Study Initiation Date and Primary Completion or Completion Dates:** 19 February 2008 to 14 December 2009

**Phase of Development**: Phase 2

**Study Objectives:** The primary objective was to evaluate the efficacy and safety/tolerability of PH-797804 in adults with moderate to severe chronic obstructive pulmonary disease (COPD; GOLD [global strategy for the diagnosis, management, and prevention of COPD] Stage II/III). The secondary objectives were: to characterize the dose response of PH-797804 in COPD patients; to explore the efficacious dose range for PH-797804 in COPD patients; to evaluate the time course of response to PH-797804 in COPD patients and to explore the pharmacokinetic-pharmacodynamic (PK-PD) relationship between dose and/or systemic PH-797804 exposure versus efficacy and/or safety/tolerability in COPD patients.

**METHODS**

**Study Design:** This was a 6-week, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of oral PH-797804 (0.5 mg, 3 mg, 6 mg, and 10 mg) in adults with moderate-to-severe COPD as defined by GOLD Stages II and III. The study comprised 10 clinic visits: a Screening visit, 2 visits during the Run-in phase to ensure stability of lung function on background therapy of ipratropium and salbutamol (Week -2 and Week -1), a Baseline/Randomization visit (Week 0), 5 visits during the double-blind treatment phase (Weeks 1, 2, 3, 4 and 6), and a follow-up visit (Week 8) after a 2-week

washout (Run-out) phase. At the beginning of the double-blind treatment phase, subjects were randomized to receive either PH-797804 (0.5 mg, 3 mg, 6 mg, or 10 mg) once daily (QD) or matching placebo. A total of 230 subjects were randomized. Single center enrollment was limited to no more than 20% of the total number of subjects.

**Number of Subjects (Planned and Analyzed):** Approximately 256 were planned, 230 subjects were randomized, and 211 were analyzed for efficacy in the full analysis set (FAS). All 230 subjects were analyzed for safety.

**Diagnosis and Main Criteria for Inclusion:** Male or female subjects ages between 40 and 80 years inclusive (females between 40 and 44 years of age were not eligible, except in the United Kingdom), with a diagnosis, for at least 6 months, of moderate to severe COPD (GOLD) and who met the criteria for Stage II-III disease (post bronchodilator forced expiratory volume in 1 second/forced vital capacity [$FEV_1$/FVC] ratio <0.7 and a post bronchodilator $FEV_1$ of 30 to 80% [inclusive] of the predicted value for age, height, race and sex using European Community for Coal and Steel [ECCS] standards). The disease must have been stable for at least 1 month before Screening, with manageable disease symptoms via short-acting bronchodilators only (ie, inhaled ipratropium bromide 2 actuations [20 μg/actuation] 4 times daily (QID) administered from a metered dose inhaler [MDI] +/-salbutamol [albuterol] rescue medication up to a maximum of 8 actuations [100 μg/actuation] QD), without reliance on other therapies including oral or inhaled corticosteroids, long-acting bronchodilators, nebulizer therapy, theophylline, or regular oxygen. Subjects must have had a smoking history of at least 10 pack-years, were current smokers or ex-smokers that gave up >6 months previously, with a body mass index (BMI) <35 $kg/m^2$ and a total body weight >40 kg.

**Study Treatment:** PH-797804 capsules and matching placebo were supplied by the sponsor. After a 1-2 week screening period and a 2-week Run-in period, subjects were required to take PH-797804 or placebo as instructed QD in the morning from Week 0 through Week 6 at about the same time each morning.

Subjects were only randomized if they could be maintained solely on the short-acting bronchodilators ipratropium bromide and salbutamol from Screening through to Baseline. All subjects were provided with short-acting bronchodilators, salbutamol (albuterol), and ipratropium bromide to use during the study as rescue and maintenance medications, respectively.

The initial randomization ratio was 1:1:1:2:1 for placebo:0.5:3:6:10 mg, respectively. An interim analysis for safety and futility was performed after 95 subjects completed double-blind treatment. At the interim analysis the randomization ratio was modified as planned with post interim subjects receiving the ratio 1:0:1:1:1 for placebo:0.5:3:6:10 mg, respectively. The lowest dose group was dropped at the interim analysis for futility.

**Efficacy Evaluations:** $FEV_1$ was the primary efficacy variable, forced expiratory volume in 6 seconds ($FEV_6$), FVC, and inspiratory capacity (IC) were secondary efficacy lung function parameters.

The IC measure was performed and captured as the maximal inspiratory volume (of 3 technically adequate tracings) from functional residual capacity (FRC) to total lung capacity (TLC). After the IC measure, subjects rested for 5 minutes before performing the forced expiratory maneuvers to determine $FEV_1$ and FVC. Sufficient forced expiratory maneuvers were performed to produce at least 3 technically adequate tracings (from a maximum of 8 maneuvers). The $FEV_1$ and FVC were recorded as absolute volumes in liters and in terms of predicted values (ECCS standards) according to age, height, race, and gender. Spirometry was performed before study drug administration at all clinic visits. Post-study drug spirometry was performed 15-30 minutes after administration of study drug at the Week 0 and Week 6 visits.

At Screening, Run-in (Weeks -2, -1) and Weeks 0 and 6, spirometry was repeated 15 to 30 minutes after inhalation of 2 actuations of salbutamol (albuterol); that is, 200 μg from an MDI plus spacer. Salbutamol (albuterol) was administered after completion of the post-study drug spirometry (Weeks 0 and 6). Percent reversibility was recorded at Screening and Run-in. Post-salbutamol (albuterol) recordings obtained at Screening and Run-in were used to assess postbronchodilator $FEV_1$/FVC ratio and postbronchodilator $FEV_1$ as a percentage predicted for age, height, sex, and race in order to confirm that the subject met the study inclusion criteria.

Secondary efficacy parameters: Twice daily, subjects performed a lung function assessment using a hand-held peak flow device, Asthma Monitor (AM2): in the morning, on waking and before taking any morning medication, and in the evening before taking the final evening dose of study maintenance medication (ipratropium bromide). Recording of peak expiratory flow rate (PEFR) started at the Screening visit and continued through the double-blind phase and ended after the Week 8 Follow-up Visit.

Subjects also evaluated the severity of their disease-related symptoms on a daily basis in the evening and at each clinic visit using a paper diary. COPD symptoms of cough, sputum production, and dyspnea were assessed daily and in addition, breathlessness was rated weekly. Symptom recording started at the Screening visit and continued through the double-blind phase and ended after the Week 8 Follow-up visit.

Subject questionnaires about dyspnea were administered at Baseline and Weeks 1, 2, 3, 4 and 6, and separate questionnaires on the overall impression of subjects and investigators as to study drug effectiveness were completed at Week 6. Dyspnea was assessed during the study using the Baseline Dyspnea Index (BDI) and Transition Dyspnea Index (TDI). The BDI was administered at Week 0 and the TDI was administered at Weeks 1, 2, 3, 4 and 6. The BDI scored the magnitude of effort, types of tasks (work and non work) that induced dyspnea, as well as the level of functional impairment. The TDI measured changes from this baseline state.

**Pharmacokinetic and Other Evaluations:** Plasma PK samples (5-mL K3 ethylenediaminetetraacetic acid [EDTA] tubes) were collected for population PK analysis. At Weeks 0 and 4 a blood sample was collected before dosing with PH-797804/placebo and another sample was collected at >3 hours and <8 hours postdose.

Other evaluations included voluntary blood sampling for biomarker analysis and genotyping. Individual subjects may have declined to contribute blood samples for these analyses and still could have participated in the clinical trial.

**Safety Evaluations:** The safety and tolerability of PH-797804 was assessed by adverse event (AE) monitoring, laboratory safety data, changes in electrocardiogram (ECG) and vital signs measurements post study drug and other safety assessments (physical exams, skin evaluations, and Tuberculosis [TB] testing).

Triplicate ECGs recordings and vital signs assessments were performed at Screening, Randomization (Week 0), and at Weeks 1, 2, 3, 4, 6, and 8 (Follow-up). Full physical examinations were performed at Screening, and Week 8, and brief physical examinations were conducted at Baseline (Week 0) and at end of treatment (Week 6). Skin lesions were evaluated as defined in the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, and subjects were tested for TB at Screening.

**Statistical Methods:** The FAS was considered the primary analysis data set and included all randomized subjects who completed at least 2 weeks of dosing and had at least 1 valid $FEV_1$ measurement during the active double-blind phase of the study. The FAS was used for all primary and secondary endpoints and was the primary population of interest. The PK analysis set consisted of those subjects who received at least 1 dose of study drug and had at least 1 quantifiable plasma concentration of PH-797804. The safety analysis set comprised all subjects who received at least 1 dose of study drug or placebo. The completer analysis set was used only for the interim analysis and included all randomized subjects who completed at least 6 weeks of dosing and completed their Week 6 $FEV_1$ tests. A per protocol analysis set (PPAS) analysis was also performed which included all subjects who had no major protocol violations and produced valid trough $FEV_1$ readings at Baseline and at the Week 6 visit.

The primary efficacy endpoint was the mean change from baseline in trough $FEV_1$ at Week 6. The primary analysis was based on the FAS (with last observation carried forward [LOCF]). The primary endpoint stated in the statistical analysis plan (SAP) was subjected to the Bayesian $E_{max}$ model (for the FAS and PPAS populations) and a repeated measures model. The $E_{max}$ models fitted make the strong assumption of monotonicity (ie, values for the mean response increase with increasing dose). The data suggested that the Bayesian $E_{max}$ model did not provide an appropriate fit, largely due to a smaller mean improvement in trough $FEV_1$ in the 10 mg dose group at Week 6 compared with the 3 mg and 6 mg dose groups. However, the SAP specified that in the event that the data did not lend itself to an $E_{max}$ model, a Normal Dynamic Linear Model (NDLM) was to be applied instead, which fitted a Bayesian spline to the data. The NDLM did not assume monotonicity of response, merely that the response at each dose was normally distributed around the mean, and that the change in mean between each dose level could be predicted using a simple linear model. The NDLM estimate of the dose-response was adjusted for baseline. The estimated response from the model for each dose was compared with placebo. Credible intervals (95%) of the effect size were presented with the posterior probability of each dose >0.075L. The main conclusion from this study was based on the non informative NDLM model results. The non informative placebo prior was assumed to be normally distributed with mean=0 and large

standard error of 1000. The non informative prior was not influential; it did not pull the observed placebo mean to a value that was previously thought to represent the placebo mean.

Continuous secondary efficacy variables (spirometry, TDI) and PD variables (C reactive protein [CRP], Clara cell 16 [CC16], fibrinogen, surfactant protein D [SPD], and interleukin-6 [IL 6]) were analyzed using a longitudinal mixed effects repeated measures model with baseline value, treatment, week and treatment by week as fixed effects terms in the model. Subject was fitted as a random effect, and the covariance structure across timepoints was estimated from the data (ie, an unstructured covariance matrix). Effects of baseline covariates (eg, measures of disease severity, degree of baseline reversibility, smoking status, and center) were investigated and included in the model as necessary. Centers were pooled at country level, and treatment by center interaction was investigated where there were enough degrees of freedom. PD endpoints were analyzed on the natural log scale. For secondary endpoints, in order to adjust for multiplicity of testing several dose groups to placebo, an average step down approach was used to control the overall alpha level at 5%. If the p-value for the average test was not significant no further testing was carried out. If p-value for the average test was statistically significant then the 6 mg contrast with placebo and the 10 mg dose group contrast with placebo were carried out. If either the 6 mg or the 10 mg group contrast was statistically significant using a 1 sided 5% test, then the 3 mg contrast with placebo was carried out. If this was statistically significant then the 0.5 mg contrast with placebo was carried out.

Plasma concentration data for PH-797804 were listed and summarized by treatment group, week and time postdose.

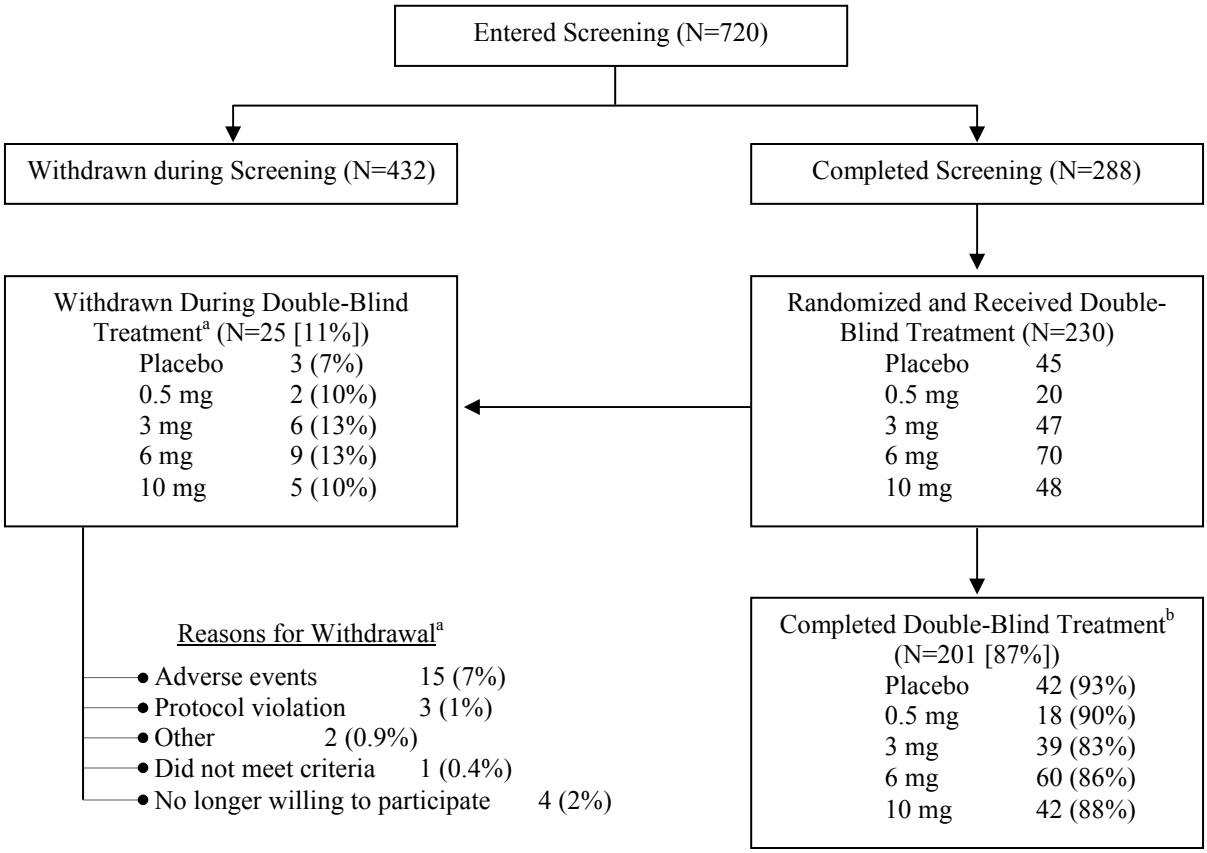
PK-PD modeling was performed to explore the link between PH-797804 exposure and $FEV_1$. A population analysis of time versus plasma concentration data of PH-797804 was performed using the nonlinear mixed effect modeling approach. In both the PK and PK-PD analyses the effects of covariates on the models were explored, and those that improved the goodness of fit were included in the models. Results from these analyses will be reported separately. PH-797804 exposure increased linearly with dose and there was no further benefit in fitting a model linking concentration to $FEV_1$ over the model fitting dose to $FEV_1$.

AE data, laboratory data, and concomitant medications were tabulated and listed but not subjected to formal statistical analysis. Other safety data were listed.

## RESULTS

**Subject Disposition and Demography:** A total of 230 subjects were randomized. Subject disposition is provided in Figure 1, and datasets analyzed are provided in Table 1.

## Figure 1. Subject Disposition




Four additional subjects were withdrawn during the follow-up period.
[a]Percentages were calculated using the total number of randomized subjects who received double-blind treatment (230 subjects).
[b]Percentages were calculated using the number of randomized and treated subjects in the corresponding treatment group.
Abbreviation: N = number of subjects

## Table 1. Data Sets Analyzed

| | Placebo | PH-797804, n (%) | | | |
|---|---|---|---|---|---|
| | | 0.5 mg | 3 mg | 6 mg | 10 mg |
| Number of subjects treated | 45 | 20 | 47 | 70 | 48 |
| Analyzed for Efficacy: | | | | | |
| Full analysis set | 42 (93.3) | 18 (90.0) | 44 (93.6) | 65 (92.9) | 42 (87.5) |
| Per-Protocol set | 31 (68.9) | 14 (70.0) | 34 (72.3) | 50 (71.4) | 32 (66.7) |
| Analyzed for Safety: | | | | | |
| Adverse events | 45 (100.0) | 20 (100.0) | 47 (100.0) | 70 (100.0) | 48 (100.0) |
| Laboratory data | 45 (100.0) | 19 (95.0) | 47 (100.0) | 70 (100.0) | 48 (100.0) |

Abbreviation: n = number of subjects

Subjects were either white or of other racial origins. Mean ages ranged between 61.7 and 65.9 years. The proportion of males and females was similar in the placebo, 0.5 mg, 3 mg, and 10 mg PH-797804 treatment groups. In the 6 mg PH-797804 treatment group 21% of the population was female and 79% male. The mean ages of males and females were similar in all treatment groups, with a combined mean age ranging between 62.4 years and 65.4 years. The age of female participants ranged from 48 to 76 years, while the age range for males was 42 to 80 years. Mean trough $FEV_1$ at baseline ranged between 1.08 L and 1.40 L, and mean percent predicted $FEV_1$ at screening ranged between 47.02% and 56.40%.

**Efficacy Results**: The primary efficacy results using NDLM (non-informative priors) are summarized in Table 2.

One subject (3 mg PH-797804) had large changes in $FEV_1$ (increase in trough $FEV_1$ of ~1 L by Week 3, returning close to baseline at Week 4, then an increase in trough $FEV_1$ of ~1 L at Week 6). There was no apparent clinical reason for this oscillation in $FEV_1$; the NDLM FAS/non-informative (NI) model was also applied excluding this subject. The estimate of the effect over placebo was reduced to 0.061 L (standard error [SE] = 0.036) with a probability of effect >0.075 L of 0.33.

**Table 2. Trough $FEV_1$ (L): NDLM Using Non-Informative Priors at Week 6 - FAS**

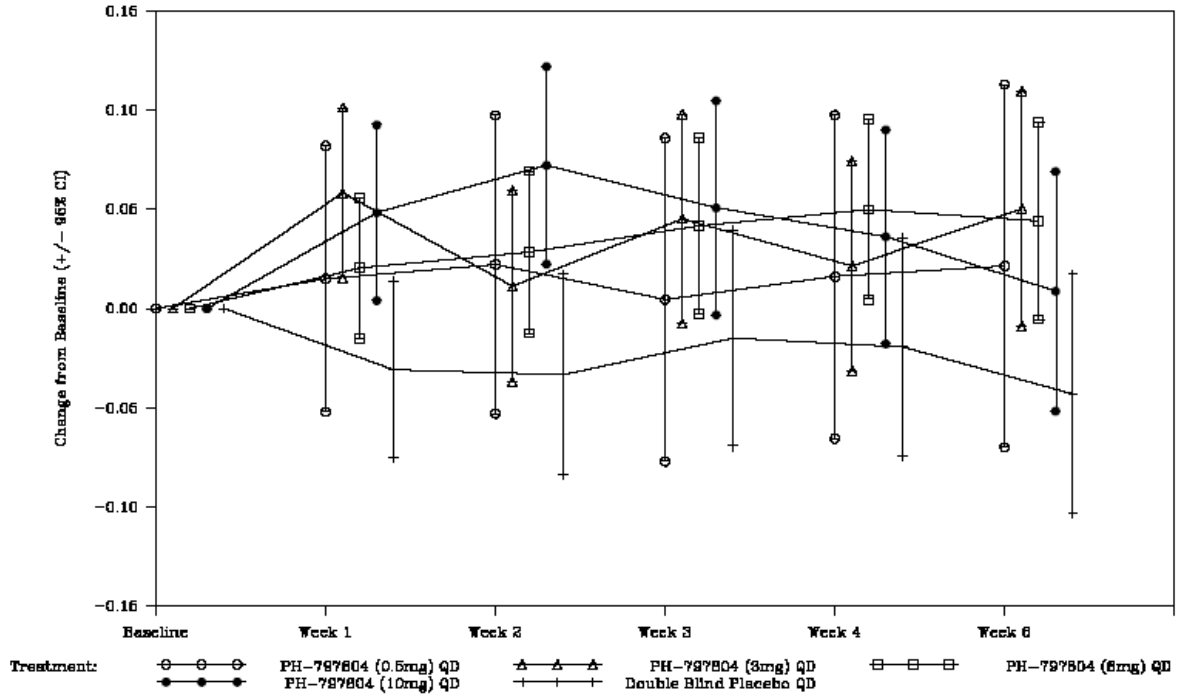
| | Placebo | PH-797804 | | | |
|---|---|---|---|---|---|
| | N = 42 | 0.5 mg N = 18 | 3 mg N = 44 | 6 mg N = 65 | 10 mg N =42 |
| Raw mean change from baseline | -0.0433 | 0.0183 | 0.0375 | 0.0371 | 0.0039 |
| SD of change from baseline | 0.1603 | 0.1278 | 0.2351 | 0.1924 | 0.2005 |
| NDLM estimated change from baseline | -0.0515 | 0.0072 | 0.0339 | 0.0405 | 0.0146 |
| SE of NDLM estimate | 0.0298 | 0.0361 | 0.0261 | 0.0221 | 0.0294 |
| 95% credible interval of dose | (-0.1099, 0.0064) | (-0.0622, 0.0818) | (-0.0166, 0.0858) | (-0.0022, 0.0845) | (-0.0423, 0.0730) |
| NDLM estimated difference from placebo | | 0.0587 | 0.0854 | 0.0920 | 0.0662 |
| 95% credible interval of effect over placebo | | (-0.0228, 0.1489) | (0.0081, 0.1644) | (0.0181, 0.1663) | (-0.0165, 0.1510) |
| Probability of effect >0 mL | | 0.9266 | 0.9842 | 0.9924 | 0.9446 |
| Probability of effect >75 mL | | 0.3314 | 0.6008 | 0.6728 | 0.4077 |

Abbreviations: $FEV_1$ = forced expiratory volume in 1 second, NDLM = Normal Dynamic Linear Model, FAS = full analysis set, SD = standard deviation, SE = standard error, mg = milligrams, mL = milliliter, N = number of subjects, L = liter

Secondary efficacy results are presented below.

Figure 2 depicts trough $FEV_1$ over time until Week 6 in the FAS. There was an improvement in $FEV_1$ over placebo as a function of time with clear evidence of a treatment effect given the separation of all active treatments from placebo. Similar results were obtained in the PPAS.

**Figure 2. Mean Change From Baseline to Week 6 (95% CI) in Trough $FEV_1$ (L) by Treatment and Week - FAS**




Abbreviations: $FEV_1$ = forced expiratory volume in 1 second, FAS = full analysis set, QD = once daily, CI = confidence interval, L = liter

PH-797804 showed a statistically significant improvement in $FEV_6$ versus placebo at Week 6 at 3 mg, 6 mg, and 10 mg showing a change from placebo of 0.115 L, SE=0.054 (p=0.0174), 0.087 L, SE=0.050 (p=0.0419), and 0.094 L, SE=0.055 (p=0.0436), respectively. Similar results were seen in the PPAS.

PH-797804 showed a statistically significant improvement in FVC versus placebo at Week 6 at 6 mg and 10 mg showing a change from placebo of 0.111 L, SE=0.054 (p=0.0217) and 0.128 L, SE=0.059 (p=0.0158). Similar results were obtained in the PPAS.

PH-797804 showed a statistically significant improvement in IC versus placebo at Week 6 at 3 mg, 6 mg, and 10 mg showing a change from placebo of 0.119 L, SE=0.057 (p=0.0193), 0.119 L, SE=0.053 (p=0.0128), and 0.096 L, SE=0.058 (p=0.0494), respectively. Results were similar to those seen in the FAS at the 6 mg (p=0.0285) and 10 mg (p=0.0534) dose levels.

For the baseline dyspnea index/transition dyspnea index, although the average of the 6 mg and 10 mg dose of PH-797804 did not show a statistical significance, it is of interest to note that PH-797804 showed an improvement in the Mahler Dyspnea Index in the 3 mg PH-797804 dose group at a 10% level of significance (0.947-point improvement, SE=0.646,

p=0.0722) and in the 6 mg PH-797804 dose group at a 5% level of significance (0.992-point improvement, SE=0.596, p=0.0487) at Week 6.

For the magnitude of effort scores, although the average of the 6 mg and 10 mg dose of PH-797804 did not show a statistical significance at the 5% level, it is of interest to note that PH-797804 showed an improvement in the magnitude of effort score in the 3 mg and 6 mg PH-797804 dose groups with a 0.495-point improvement, SE=0.261 at 3 mg dose level (p=0.0294) and a 0.475-point improvement, SE=0.240 at the 6 mg dose level (p=0.0248) at Week 6.

For clinicians' and subjects' global impression of change, clinicians noted an improvement over placebo at the 0.5 mg, 3 mg, and 6 mg PH-797804 dose levels, and subjects noted an improvement over placebo at the 3 mg and 6 mg PH-797804 dose levels. The clinicians' scores indicated a greater global impression of change compared to subjects.

**Pharmacokinetic, Pharmacodynamic, and/or Other Results**: Mean and median observed PH-797804 plasma concentrations increased with increasing dose levels, although the increases were not dose proportional.

CRP results indicated a potential anti-inflammatory effect at 3 mg, 6 mg and 10 mg doses, with statistically significant differences from placebo observed in the ratio of the means of 0.633 [95% 1 sided upper confidence limit (CL) =0.954] (p=0.0334), 0.588 [CL=0.861] (p=0.0114), and 0.594 [CL=0.905] (p=0.0212), respectively; the effect on CRP was maintained throughout the 6 week dosing period. As CRP is an established biomarker of inflammation, these results demonstrated that PH-797804 significantly reduced inflammation when compared with the placebo dose.

No statistically significant differences from placebo were observed for fibrinogen, surfactant protein D, or CC16.

**Safety Results:** There were no deaths reported in this study. No subject was discontinued temporarily or had a dose reduction due to AEs. Three subjects reported treatment-related serious adverse events (SAEs) during the study: 1 subject reported upper gastrointestinal (GI) hemorrhage, 1 subject reported worsening right and left bundle branch block, and 1 subject reported duodenal ulcer. Each of these subjects discontinued due to treatment-related AEs. An additional 5 subjects discontinued due to treatment-related rashes ranging from mild to severe in intensity. There was a greater incidence of treatment-related AEs after dosing with 6 mg and 10 mg PH-797804 (19 [27.1%] and 11 [22.9%], respectively) compared with 0.5 mg and 3 mg PH-797804 and placebo (2 [10.0%], 4 [8.5%], and 3 [6.7%], respectively). Treatment-related severe AEs were more frequent in the 6 mg PH-797804 treatment group than in the other treatment groups (3 [4.3%]).

Table 3 summarizes the most commonly reported all-causality treatment-emergent AEs (AEs occurring in at least 2 subjects).

**Table 3. All-Causality Treatment-Emergent Adverse Events in ≥2 Subjects in Any Treatment Group**

| MedDRA Preferred Term | Number (%) of Subjects | | | | |
|---|---|---|---|---|---|
| | Placebo | PH-797804 | | | |
| | N = 45 | 0.5 mg N = 20 | 3 mg N = 47 | 6 mg N = 70 | 10 mg N =48 |
| Chronic obstructive pulmonary disease[a] | 5 (11.1) | 0 | 3 (6.4) | 1 (1.4) | 6 (12.5) |
| Rash | 1 (2.2) | 1 (5.0) | 3 (6.4) | 9 (12.9)[b] | 1 (2.1) |
| Nasopharyngitis | 2 (4.4) | 0 | 5 (10.6) | 3 (4.3) | 0 |
| Diarrhoea | 0 | 0 | 1 (2.1) | 3 (4.3) | 2 (4.2) |
| Headache | 1 (2.2) | 0 | 0 | 5 (7.1) | 0 |
| Tremor | 0 | 0 | 0 | 1 (1.4) | 4 (8.3) |
| Pharyngitis | 1 (2.2) | 0 | 0 | 2 (2.9) | 1 (2.1) |
| Urinary tract infection | 1 (2.2) | 0 | 0 | 1 (1.4) | 2 (4.2) |
| Alanine aminotransferase increased[c] | 0 | 0 | 1 (2.1) | 1 (1.4) | 2 (4.2) |
| Dizziness | 2 (4.4) | 0 | 0 | 0 | 1 (2.1) |
| Dyspepsia | 1 (2.2) | 0 | 0 | 2 (2.9) | 0 |
| Fatigue | 0 | 0 | 0 | 0 | 2 (4.2) |
| Nausea | 0 | 0 | 0 | 2 (2.9) | 1 (2.1) |
| Arthralgia | 0 | 0 | 0 | 2 (2.9) | 0 |
| Bundle branch block left | 0 | 0 | 0 | 2 (2.9) | 0 |
| Bundle branch block right | 0 | 0 | 0 | 2 (2.9) | 0 |
| Chest pain | 0 | 0 | 0 | 0 | 2 (4.2) |
| Dry skin | 0 | 0 | 0 | 2 (2.9) | 0 |
| Syncope | 0 | 0 | 0 | 2 (2.9) | 0 |

[a]COPD exacerbation
[b]Includes 2 subjects who had preferred term "rash generalized" reported.
[c]The maximum ALT increase was <2×ULN
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 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 is summarized. Missing baseline severities were imputed as mild.
Includes data up to 999 days after last dose of study drug.
MedDRA (v12.1) coding dictionary applied.
Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, COPD = Chronic obstructive pulmonary disease, TESS = treatment-emergent signs and symptoms, N = number of subjects, ULN = upper limit of normal, ALT = alanine aminotransferase

For reporting purposes, the term "rash" includes the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms rash, rash generalized, rash macular, rash pustular, dermatitis, dermatitis acneiform, and pruritus. A total of 19 subjects reported 21 events of rash during the study, 14 of which (in 12 subjects) were considered to be related to study drug by the investigator. A total of 5 subjects were withdrawn from the study by the investigator due to rash.

Table 4 lists permanent discontinuations due to AEs, and Table 5 lists SAEs that occurred during the study.

## Table 4. Permanent Discontinuations Due to Adverse Events

| MedDRA Preferred Term | Study Start/Stop Day | Severity/ Outcome | Study Drug Action/ Causality |
|---|---|---|---|
| **3 mg PH-797804** | | | |
| Chronic obstructive pulmonary disease (exacerbation)[a] | 17/ 111 | Moderate/Resolved | PD/NR (due to disease under study) |
| Rash | 2/[115] | Moderate/Resolved | PD/R |
| Influenza | 4/17 | Mild/Resolved | PD/NR (due to other illness - influenza) |
| **6 mg PH-797804** | | | |
| Upper gastrointestinal hemorrhage [a] | 2/2 | Moderate/Resolved | PD/R |
| Pyelonephritis (right) [a] | 14/28 | Severe/Resolved | PD/NR (due to other infection) |
| Upper respiratory tract infection | 13/29 | Moderate/Resolved | PD/NR (due to disease under study) |
| Bundle branch block left (worsening of left anterior fascicular block) [a] | 20/27 | Severe/Resolved | PD/R |
| Atrial fibrillation | 15/22 | Mild/Resolved | PD/NR (due to concomitant indapamide) |
| Rash generalized (cutaneous) | 13/ 44 | Severe/Resolved | PD/R |
| Rash generalized (cutaneous) | 38/ 49 | Mild/Resolved | No action taken/R |
| Peak expiratory flow rate decreased (progressive decline) | 15/[>15] | Moderate/Still present | PD/NR (due to disease under study) |
| Duodenal ulcer (x2) [a] | 30/ 38 | Severe/Resolved | PD/R |
| Rash | 25/ 44 | Mild/Resolved | PD/R |
| **10 mg PH-797804** | | | |
| Chronic obstructive pulmonary disease (exacerbation) | 47/ 61 | Moderate/Resolved | No action taken /NR (due to disease under study) |
| Rash macular | 29/ 35 | Mild/Resolved | PD/R |
| Chronic obstructive pulmonary disease (exacerbation)[a] | 10/[>10] | Severe/Still present | PD/NR (due to disease under study) |
| **Placebo** | | | |
| Chronic obstructive pulmonary disease (exacerbation) | 18/ 31 | Moderate/Resolved | PD/NR (due to disease under study) |

Study start day was relative to start of study treatment. First day of study treatment = Day 1
[ ] values in brackets were imputed from incomplete dates and times.
MedDRA (v12.1) coding dictionary applied.
Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, PD = permanently discontinued, NR = not related to study drug, R = related to study drug
[a] Serious adverse event according to investigator's assessment

## Table 5. Serious Adverse Events (All Causality)

| Treatment Group | Serious Adverse Event MedDRA Preferred Term (Investigator Term) | Severity | Study Start/Stop Day | Causality; Subject Action | Outcome |
|---|---|---|---|---|---|
| **PH-797804** | | | | | |
| 3 mg | Chronic obstructive pulmonary disease (COPD exacerbation) | Moderate | 17/111 | Disease under study; treatment given, permanently discontinued study | Resolved |
| 6 mg | Upper gastrointestinal hemorrhage (upper gastrointestinal bleed) | Moderate | 2/2 | Study drug; endoscopy and anastomotic biopsy; permanently discontinued | Resolved |
| | Pyelonephritis (right pyelonephritis) | Severe | 14/28 | Other infection; treatment given, discontinued study | Resolved |
| | Bundle branch block left (left anterior fascicular block worsening) | Severe | 20/27 | Study drug; permanently discontinued | Resolved |
| | Bundle branch block right (incomplete right bundle branch block worsening) | Severe | 20/27 | Study drug; insert pacemaker; permanently discontinued | Resolved |
| | Duodenal ulcer (duodenal ulcer x 2) | Severe | 30/38 | Study drug; treatment given, permanently discontinued | Resolved |
| 10 mg | Chronic obstructive pulmonary disease (COPD exacerbation) | Severe | 10/[>10] | Disease under study; permanently discontinued | Still present |
| **Placebo** | Lung neoplasm malignant (lung cancer) | Severe | 1/73 | Cancer; permanently discontinued | Resolved |
| | Cholelithiasis (cholelithiasis) | Severe | 51/53 | Cholelithiasis; no action taken | Resolved |
| | Diabetes mellitus (worsening of diabetes mellitus) | Severe | 51/[>68] | Diabetes mellitus; treatment given | Still present |

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, COPD = chronic obstructive pulmonary disease
MedDRA (v12.1) coding dictionary applied.
[ ] Value in brackets was imputed from incomplete dates and times.

There were no large changes to liver function tests in subjects receiving PH-797804 or significant changes to other clinical chemistry or hematology parameters.

Table 6 summarizes clinically significant laboratory abnormalities reported as AEs. Overall, more laboratory abnormalities occurred in the 10 mg PH-797804 dose group compared to the other dose groups. Alanine aminotransferase increased (MedDRA term) was the only clinical laboratory AE that was judged related to the study treatment.

**Table 6. Clinically Significant Laboratory Abnormalities (All Causalities)**

| MedDRA Preferred Term | Number (%) of Subjects | | | | |
|---|---|---|---|---|---|
| | Placebo | PH-797804 | | | |
| | N = 45 | 0.5 mg N = 20 | 3 mg N = 47 | 6 mg N = 70 | 10 mg N =48 |
| Alanine aminotransferase increased | 0 | 0 | 1 (2.1) | 1 (1.4) | 2 (4.2) |
| Aspartate aminotransferase increased | 0 | 0 | 0 | 0 | 1 (2.1) |
| Blood calcium increased | 0 | 0 | 0 | 0 | 1 (2.1) |
| Blood glucose increased | 0 | 0 | 1 (2.1) | 1 (1.4) | 0 |
| Blood urine present | 1 (2.2) | 0 | 0 | 0 | 0 |
| Gamma-glutamyltransferase increased | 0 | 0 | 0 | 0 | 1 (2.1) |

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 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 is summarized. Missing baseline severities were imputed as mild.
Includes data up to 999 days after last dose of study drug.
MedDRA (v12.1) coding dictionary applied.
Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, TESS = treatment-emergent signs and symptoms, N = number of subjects

Changes from baseline for QT intervals increased over time at the higher PH-797804 dose intervals (between 3 mg and 10 mg). Mean QTcF changes from baseline to Week 6 in the PH-797804 active dose groups (3 mg through 10 mg) were greater than in the placebo treatment group and the 0.5 mg PH-797804 treatment group. Mean changes from baseline ranged between 5.6 msec and 13.5 msec in subjects who received 3 mg through 10 mg PH-797804 (with the greatest change in the 10 mg dose group), compared with a range between -1.4 msec and 2.0 msec in the placebo group and between -0.8 msec and 7.1 msec in the 0.5 mg treatment group. Mean changes from baseline at Week 8 ranged between -5.1 msec and 0.1 msec across all dose groups.

Two clinically significant ECG abnormalities occurred: One white 56-year-old male who received 3 mg PH-797804, experienced mild electrocardiogram T wave abnormality (changes in the inferior waves on the ECG recording) starting on Day 15 and lasting until Day 57. Creatine kinase (CK) and troponin tests were conducted, and the results were normal. The investigator attributed this AE to other, nonspecific causes and continued to follow the subject closely. In addition, a white 60-year-old male who received 10 mg PH-797804, experienced mild electrocardiogram T wave inversion starting on Day 29 that was still ongoing at the end of the study. CK and troponin tests were conducted, and the results were negative. The investigator attributed this AE to the study drug.

Table 7 summarizes the number (%) of subjects who had ECG results meeting predefined safety criteria. No subjects had QTcF intervals exceeding 500 msec.

**Table 7. Categorization of Electrocardiogram Data**

| Parameter (msec) | Criteria | Number (%) of Subjects | | | | |
|---|---|---|---|---|---|---|
| | | Placebo | PH-797804 | | | |
| | | N = 45 | 0.5 mg N = 20 | 3 mg N = 47 | 6 mg N = 70 | 10 mg N =48 |
| Maximum PR interval | >=300 | 2 (4.4) | 0 | 0 | 1 (1.4) | 0 |
| Maximum QRS complex | >=200 | 1 (2.2) | 0 | 0 | 0 | 0 |
| Maximum QT interval | >=500 | 0 | 0 | 0 | 0 | 0 |
| Maximum QTcF interval | 450-<480 | 1 (2.2) | 0 | 2 (4.3) | 7 (10.0) | 0 |
| | 480-<500 | 0 | 0 | 0 | 0 | 1 (2.1) |
| | >=500 | 0 | 0 | 0 | 0 | 0 |

Abbreviations: PR = time interval from onset of atrial depolarization (P wave) to onset of QRS complex, QRS = duration of ventricular muscle depolarization, QT = the duration of ventricular depolarization and repolarization, QTcF = QT corrected for heart rate using Fridericia's formula, N = number of subjects, msec = milliseconds, mg = milligrams

Table 8 summarizes the number (%) of subjects with predefined QTcF increases from baseline at any one measurement. Most subjects had QTcF changes from baseline below 30 msec. The percentage of subjects with QTcF increases from baseline between 30 and 60 msec was higher in the 3 mg through 10 mg PH-797804 dose groups. Table 9 presents subjects with QTcF increases from baseline of at least 60 msec.

**Table 8. Categorization of Electrocardiogram Maximum Increase from Baseline**

| Parameter (msec) | Criteria | Number (%) of Subjects | | | | |
|---|---|---|---|---|---|---|
| | | Placebo | PH-797804 | | | |
| | | N = 45 | 0.5 mg N = 19 | 3 mg N = 47 | 6 mg N = 67 | 10 mg N =46 |
| Maximum QTcF interval | Change<30 | 37 (82.2) | 17 (89.5) | 32 (68.1) | 48 (71.6) | 34 (73.9) |
| | 30<=Change<60 | 8 (17.8) | 2 (10.5) | 11 (23.4) | 16 (23.9) | 12 (26.1) |
| | Change>=60 | 0 | 0 | 4 (8.5) | 3 (4.5) | 0 |

Baseline was defined to be mean of a range of measurements.
Means of replicate values were used in the report.
Unplanned readings were excluded from the presentation.
Abbreviations: QT = the duration of ventricular depolarization and repolarization, QTcF = QT corrected for heart rate using Fridericia's formula, N = number of subjects, msec = milliseconds

**Table 9. QTcF Changes From Baseline of at Least 60 msec**

| | | | Parameters (msec) | |
|---|---|---|---|---|
| **Treatment** | **Subject** | **Study Week** | **QTcF Change** | **QTcF Result** |
| **PH-797804** | | | | |
| 3 mg | 10071008 | 8 | 66.67 | 452 |
| | 10441012 | 2 | 63.00 | 441 |
| | 10441014 | 1 | 60.33 | 416 |
| | 10621038 | 3 | 62.33 | 435 |
| | | | 63.33 | 436 |
| 6 mg | 10071004 | 2 | 61.67 | 429 |
| | 10351019 | 2 | 60.67 | 449 |
| | | | 61.67 | 450 |
| | 10371019 | 6 | 61.33 | 426 |

Baseline was defined to be mean of a range of measurements.
Means of replicate values were used in the report. The changes from baseline were derived for each individual post baseline ECG value as x-m(b),where x was an individual replicate ECG value and m(b) was the mean baseline value based on averaging the 3 baseline replicates.
Unplanned readings were excluded from the presentation.
Abbreviations: QT = the duration of ventricular depolarization and repolarization, QTcF = QT corrected for heart rate using Fridericia's formula, ECG = electrocardiogram, mg = milligram, msec = milliseconds

No marked mean vital signs results or changes from baseline were observed

**Conclusions:**

- PH-797804 demonstrated a statistically meaningful improvement over placebo in the change from baseline in trough $FEV_1$ and other secondary endpoints such as FVC, $FEV_6$, and IC and meaningful improvements in TDI and rescue medicine use following 6 weeks of dosing in subjects with moderate to severe COPD.
    - PH-797804 gave improvements in trough $FEV_1$ versus placebo at all dose levels. The 0.5 mg dose of PH-797804 was stopped for futility at the interim analysis and the largest mean effect at Week 6 on trough $FEV_1$ was observed at the 6 mg dose (0.092 L [95% credible interval=0.018, 0.166]). This met the pre-specified criteria of >75 mL improvement over placebo.
    - There was a clear drug effect over Week 1 to Week 6 although maximal effect differed between dose groups with an apparent decrease in the mean effect of 10 mg PH-797804 on $FEV_1$ by Week 6.
    - PH-797804 demonstrated a clinically meaningful improvement of approximately 1 point (SE=0.6) at Week 6 in the TDI at doses of 3 mg and 6 mg.
    - PH-797804 demonstrated a statistically significant improvement in IC, $FEV_6$ and FVC.

- The PH-797804 6 mg dose group used less rescue medicine compared with placebo with a mean daily use of 0.659 (SE=0.322) fewer actuations of salbutamol, at Week 6 compared to placebo.

- Other variables, including Global Impression of Change, showed numerical improvements over placebo.

- There was no clear relationship between plasma exposure to PH-797804 and the efficacy endpoints in this study.

- PH-797804 reduced CRP at doses above 0.5 mg, indicating an anti-inflammatory effect. This effect was maintained over the 6 week period of the study. There was no clear effect on other markers of inflammation, which were all highly variable.

- PH-797804 was safe and well tolerated at all doses administered in the study. The greatest incidence of adverse events was observed at the 6 and 10 mg doses of PH-797804.

  - PH-797804 adverse events of interest for future investigation include rash, GI events and ECG abnormalities.