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COMPOUND NUMBER: PH-797804

PROTOCOL NO.: A6631029

PROTOCOL TITLE: A Phase II, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Once-Daily Orally Administered PH-797804 for 12-Weeks in Adults With Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD) on a Background of Salmeterol Xinafoate/Fluticasone Propionate Combination

Study Centers: Sixty seven (67) centers took part in the study and randomized subjects; 17 in the United States, 6 each in Slovakia and Canada, 5 each in Bulgaria, Czech Republic, and South Africa, 4 each in Hungary and Sweden, 3 each in Argentina and Poland, 2 each in the United Kingdom, Australia, India and New Zealand, and 1 in Chile.

Study Initiation Date and Final Completion Date: 01 June 2011 to 25 June 2012

Phase of Development: Phase 2

Study Objectives: To evaluate the efficacy and safety/tolerability of 12 weeks administration of PH-797804 in adults with moderate to severe COPD (Global Initiative for Chronic Obstructive Lung Disease [GOLD] Stage II/III) on a background of salmeterol xinafoate/fluticasone propionate combination (SFC).

METHODS

Study Design: This was a 12-week, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of oral PH-797804 (6 mg) in adult subjects with moderate to severe COPD as defined by GOLD Stages II/III on a background combination of long-acting β_2 receptor agonist (LABA) and inhaled corticosteroid (ICS). The study comprised 8 clinic visits: a Screening visit (Week -4, Visit 1), a run-in phase (Week -1, Visit 2) in order to establish baseline values for spirometry in subjects stabilized on rescue/background therapy of salbutamol, a randomization visit (Week 0, Visit 3), 4 visits during the double-blind treatment phase (Weeks 2, 6, 10, and 12; Visits 4, 5, 6, and 7 respectively), and a follow-up visit (Week 14, Visit 8). At the beginning of the double-blind treatment phase, subjects were randomized to receive either PH-797804 6 mg once daily (QD) + SFC twice a day (BID) or matching placebo + SFC BID.

A schedule of activities is provided in Table 1.

Table 1. Schedule of Activities

	Screen	Run-in	Double-Blind Treatment Phase					Follow Up/ET
Study Week	**-4**	**-1**	**0**	**2**	**6**	**10**	**12**	**14**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Informed consent	X							
IVRS/IWRS registration/contact	X		X	X	X	X		X
Medical history/demographics	X							
Concomitant medication review	X	X	X	X	X	X	X	X
Physical examination[a]	X		X				X	X
Blood pressure/pulse rate[b]	X		X	X	X	X	X	X
Review inclusion/exclusion criteria (and FEV_1 randomization criteria Week 0)	X	X	X					
Review of adverse events		X	X	X	X	X	X	X
Chest x-ray (if none within 3 months)	X							
TB testing	X							
12-lead resting ECG[c]	X		X	X	X	X	X	X
Lab safety tests (hematology, chemistry)[d]	X		X	X	X	X	X	X
Routine urinalysis[e]	X		X	X			X	X
Samples for Sponsor's exploratory research biobank[f]	X		X	X	X		X	
CRQ-SAS			X	X	X	X	X	X
Baseline/Transition Dyspnea Index			X	X	X	X	X	X
Daily diary download and review (symptom and bronchodilator use)		X	X	X	X	X	X	X
Spirometry (trough)[g]	X	X	X	X	X	X	X	X
Randomization			X					
Study drug administered during clinic visit			X	X	X	X	X	
Spirometry (post study drug)[h]			X				X	
Salbutamol administered at clinic visit[i]	X	X	X				X	
Spirometry (post salbutamol)[j]	X	X	X				X	
Blood for biomarkers			X	X	X	X	X	X
PK – trough			X	X	X	X	X	X
PK – post dose			X	X	X	X	X	
Study drug dispensed			X	X	X	X		
Dispense salmeterol fluticasone combination	X	X	X	X	X	X	X	
Dispense salbutamol	X	X	X	X	X	X	X	
Study drug return and accountability				X	X	X	X	
Train subject in use of electronic daily diary, log subject on device and hand out device[k]	X							
Provide diary	X	X	X	X	X	X	X	
Global Impression of Change (physician and subject)							X	

CRQ-SAS = chronic respiratory questionnaire self-administered standardized; ECG = electrocardiogram; ET = end of treatment; FEV_1 = forced expiratory volume in 1 second; IVRS/IWRS = interactive voice response system/interactive web response system; lab = laboratory; PK = pharmacokinetics, QTcF = QT corrected for heart rate using Fridericia's formula; TB = tuberculosis.

a. Only a brief physical examination was required. Full physical examinations were required at Screening and Week 14 or end of study visit if earlier than Week 14.
b. Vital signs (blood pressure and pulse) were collected prior to blood sample or spirometry.
c. ECGs were to be obtained in triplicate at each visit. Central over-read of ECGs was to be performed in the event that a QTcF >500 ms during the active treatment period or a change from Baseline ≥60 ms. If a QTcF was >450 ms at Screening or Week 0 the subject was not to be included.
d. Liver function tests were to be monitored at each clinic visit and available for review to the Investigator and the Sponsor. Follicle stimulating hormone was to be determined for amenorrheic women (that did not have documented evidence of bilateral oophrectomy or hysterectomy) at Screening.

Table 1. Schedule of Activities

e.	Urine was to be collected at Screening, Week 0, Week 2 and Week 12 only (was not required at other weeks unless abnormal at Week 2). Urine was to be collected in case of early termination. At Follow-up visit only, samples were to be collected if abnormalities detected at Week 12.
f.	Exploratory Research which was performed on a voluntary basis only.
g.	At the Week 12 visit only, replicate trough spirometry measurements were to be collected 30 to 60 minutes after initial spirometry assessment, and before administration of study drug.
h.	Post-study drug spirometry was to be performed 15 to 30 minutes after dosing with study drug.
i.	Salbutamol (albuterol) was to be administered after all spirometry related to study drug and after any scheduled (or non-scheduled) ECGs had been completed.
j.	Post-salbutamol spirometry was to be performed 15 to 30 minutes after salbutamol (albuterol) dosing.
k.	Electronic Daily Diary was a Personal Digital Assistant that contained the EXACT-PRO, and rescue medication use diary. It was to be completed daily at home by subjects.

Number of Subjects (Planned and Analyzed): It was planned to randomize 164 subjects per treatment group to ensure 140 subjects per treatment group completed 12 weeks of double-blind treatment. A total of 689 subjects were screened for the study, out of which 189 subjects were assigned to treatment with PH-797804 and 187 subjects were assigned to treatment with placebo. All treated subjects were analyzed for efficacy and safety.

Diagnosis and Main Criteria for Inclusion: Male or female (of non-childbearing potential) subjects between, and including, the ages of 40 and 80 years, with a diagnosis, for at least 6 months, of moderate to severe COPD (GOLD) and who met the criteria for Stage II/III disease. Subjects were to have a smoking history of at least 10 pack-years and were either current smokers or were ex-smokers who had abstained from smoking for at least 6 months. Subjects were to have been treated with LABA/ICS combination for at least 1 month prior to Screening.

Main Exclusion Criteria: A COPD exacerbation that required treatment with oral steroids or hospitalization for the treatment of COPD within 3 months of screening; history or presence of significant cardiovascular disease; electrocardiogram (ECGs) abnormalities; significant concomitant clinical disease that could have interfered with the conduct, safety or interpretation of results of this study; evidence of organ or blood disorders.

Study Treatment: PH-797804 and matching placebo were provided as 6 mg material sparing tablets or matching placebo for oral administration.

Study medication was to be administered to the subject in the clinic on the morning of clinic visits; all other dosing was performed by the subject outside of the clinic. PH-797804/placebo was to be administered QD in the morning, orally. SFC was to be administered BID by inhalation.

Subjects were only to be randomized if they could be maintained solely on the SFC and the short acting bronchodilator salbutamol from Screening through to Baseline (Week 0) of the study. All subjects were issued with SFC and salbutamol inhalers at Screening and run in Week -1. Subjects were to be issued with supplies of the SFC therapy at Weeks 0, 2, 6, 10, and 12 for use as described below. Subjects were to continue to take SFC until Week 14. All subjects were to use SFC BID as maintenance therapy from Screening (Week -4) through to Week 14.

Rescue medication was provided to all subjects at each clinic visit. Salbutamol (albuterol) was to be supplied as metered dose inhalers (MDIs) (100 µg/actuation); 200 actuations/MDI. Subjects were to use 1 to 2 puffs as needed for rescue therapy. All rescue medication use was to be recorded daily in the subject diary.

Efficacy and Safety Endpoints: The primary efficacy endpoint was the comparison between treatments in the change from Baseline in pre-bronchodilator, trough (prior to administration of study medication and other back ground medications) forced expiratory volume in 1 second (FEV_1) at Week 12.

Secondary efficacy endpoints evaluated were:

- Change from Baseline in pre-bronchodilator, trough FEV_1, forced expiratory volume in 6 seconds (FEV_6), forced vital capacity (FVC) and inspiratory capacity (IC) at 2, 4, 6, 10, and 12 weeks of therapy.
- Average change from Baseline in pre-bronchodilator, trough FEV_1, FEV_6, FVC and IC over 12 weeks of therapy.
- Change from Baseline in post-study drug, pre-bronchodilator (ie, post study drug minus pre study drug) FEV_1, FEV_6, FVC, and IC at Week 0 and after 12 weeks of therapy.
- Change from Baseline in post-bronchodilator minus pre-bronchodilator FEV_1, FEV_6, FVC, and IC at Week 0 and after 12 weeks of therapy.
- Change from Baseline in Mahler Dyspnea Index (Baseline Dyspnea Index [BDI]/Transient Dyspnea Index [TDI]) at Weeks 2, 4, 6, 10, and 12.
- Change from Baseline in COPD symptoms (EXACT-respiratory symptom [E-RS] diary) over 12 weeks of therapy.
- Rescue bronchodilator use (per daily diary) over 12 weeks of therapy.
- Change from Baseline in Chronic Respiratory Questionnaire – Self-Administered Standardized (CRQ-SAS) at Weeks 2, 6, 10, and 12.
- Global Impression of Change (physician and subject) at Week 12.

Safety endpoints included adverse events (AEs), laboratory safety data, change in ECGs measurements post study medication and change in vital signs (pulse and blood pressure) post study medication (assessed at the time points indicated in Table 1).

Safety Evaluations: The safety and tolerability of PH-797804 was assessed by AE monitoring, laboratory safety data, changes in ECG and vital signs measurements post study medication and other safety assessments (physical examinations, skin evaluations, and tuberculosis testing. These were assessed at the time points indicated in Table 1.

Statistical Methods: The population sets analyzed were as follows:

Full Analysis Set (FAS): Included all randomized subjects, who 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 endpoint analyses.

Per Protocol Analysis Set (PP): Included all subjects who had no major protocol violations and produced valid trough FEV_1 readings at both Baseline and the Week 12 visit.

Safety Analysis Set: Included all subjects randomized, regardless of whether they had efficacy data or received study treatment.

The primary endpoint was analyzed using a longitudinal mixed effects 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 time points was estimated from the data (ie, an unstructured covariance matrix). No classical hypothesis testing was conducted; Bayesian (posterior) probabilities were calculated. The probabilities of passing the decision criteria for efficacy at the end of the study were calculated. The criteria were based on a Bayesian interpretation of the results assuming a non-informative prior and were thus based on classical analysis of the results:

- C1: PH-797804 (6 mg) has ≥90% probability of getting >0 mL over placebo in change from Baseline FEV_1.
- C2a: PH-797804 (6 mg) has ≥50% probability of 50 mL improvement in FEV_1 and 90% probability of getting >0 mL.
- C2b: PH-797804 (6 mg) has ≥90% probability of getting >0 over placebo in BDI/TDI.
- C2c: PH-797804 (6 mg) has ≥90% probability of getting >0 over placebo in Chronic Respiratory Questionnaire-Quality of Life (CRQ-QoL).
- C2d: PH-797804 (6 mg) has ≥90% probability of getting <1 in the ratio of treatment to placebo in the number of puffs of rescue short acting bronchodilator.

A separate sensitivity analysis fit the above model together with terms for smoking status and country, and the 2-way interactions of smoking status with treatment and country by treatment. No multiplicity adjustments were required, since this issue was addressed implicitly in the Bayesian analysis. The primary time point of interest was at Week 12. The treatment effect over placebo at this time point, from the above model, was estimated, together with the probability of passing C1 and C2a decision criteria. From the longitudinal mixed effects model, estimates of the treatment effect were reported at each time point along with associated 1-sided 90% confidence intervals (CIs). From the longitudinal mixed effects model, a secondary analysis estimated the treatment effect over placebo averaged over time. This contributed to the secondary endpoint, the average change from Baseline in pre-bronchodilator, trough FEV_1, FEV_6, FVC, and IC over 12 weeks of therapy.

Change from Baseline in trough FEV_6, FVC, and IC at Weeks 2, 6, 10, and 12 was compared to placebo using the model described for the primary endpoint.

The post study drug spirometry measured the acute effects of single and multiple doses. The post study drug spirometry minus the spirometry values (FEV_1, FEV_6, FVC, and IC) immediately prior to study drug values were calculated at Weeks 0 and 12. Repeated FEV_1 values taken prior to study drug at Week 12 were averaged prior to calculating this difference. The acute effect of single dose of study drug at Week 0 was analyzed by examining this difference. An analysis of variance of the effect at Week 0 was conducted with treatment as the factor of interest. The same model was applied for Week 12 data. Additionally the acute effect of multiple doses of study drug was examined by analyzing the Week 12 – Week 0 changes of these differences.

The post-bronchodilator spirometry minus the post study drug (ie, immediately prior to bronchodilator) spirometry values (FEV_1, FEV_6, FVC, and IC) were calculated at Weeks 0 and 12. These changes at Week 12 were compared to the corresponding changes at Week 0. An analysis of variance of the effect at Week 0 was conducted with treatment as the factor of interest. The same model was applied for Week 12 data.

The Mahler TDI Total Focal Score at Weeks 2, 6, 10 and 12 was analyzed using the mixed effects model described for the primary endpoint with BDI at Week 0 as a covariate. The Total Focal Score was derived from the BDI and TDI indices. The treatment effect over placebo at Week 12 was estimated together with the probability of passing C2b decision criteria. The 3 TDI subscales were summarized descriptively.

COPD Symptoms (E-RS), number of weekly puffs of rescue bronchodilator and CRQ-SAS were analyzed using the longitudinal mixed effects model described for the primary analysis.

The Global Impression of Change (physician and subject) was analyzed using proportional odds logistic regression with treatment as the factor of interest in the model.

All safety data (AEs, laboratory, vital signs, ECG) were summarized using descriptive statistics.

RESULTS

Subject Disposition and Demography: Of 689 subjects screened for the study, 189 subjects were assigned to treatment with PH-797804 and 187 subjects were assigned to treatment with placebo. Table 2 summarizes subject disposition for the study.

Table 2. Subject Disposition

Number of Subjects	PH-797804 6 mg	Placebo
Screened, N = 689		
Assigned to study treatment, N	189	187
Treated, n	189	187
Completed, n (%)	154 (81.5)	165 (88.2)
Discontinued, n (%)	35 (18.5)	22 (11.8)
Withdrawn during active/double-blind treatment period, n (%)	35 (18.5)	20 (10.7)
Withdrawn during post-therapy follow up period, n (%)	0 (0.0)	2 (1.1)
Reasons for discontinuation		
Subject died	1 (0.5)	0 (0.0)
AEs related to study drug	13 (6.9)	5 (2.7)
AEs not related to study drug	13 (6.9)	13 (7.0)
Did not meet entrance criteria	1 (0.5)	0 (0.0)
No longer willing to participate	1 (0.5)	0 (0.0)
Other	1 (0.5)	0 (0.0)
Protocol violation	5 (2.6)	3 (1.6)

AEs = adverse events; N = number of subjects; n = number of subjects with specified criteria.

Table 3 summarizes the subjects analyzed for safety and efficacy.

Table 3. Data Sets Analyzed

	PH-797804 6 mg	Placebo
Number of subjects treated	189	187
Analyzed for efficacy		
Full analysis set	189 (100.0)	187 (100.0)
Per protocol set	147 (77.8)	157 (84.0)
Analyzed for safety		
Adverse events	189 (100.0)	187 (100.0)
Laboratory data	185 (97.9)	186 (99.5)
Vital signs	189 (100.0)	187 (100.0)
ECG	189 (100.0)	187 (100.0)
Analyzed for pharmacokinetics	188 (99.5)	0

ECG = electrocardiogram.

Table 4 summarizes the demographic characteristics of subjects participating in this study and trough FEV_1 at Baseline.

Table 4. Summary of Demographic and Baseline Characteristics

	PH-797804 6 mg (N=189)	Placebo (N=187)
Gender (n)		
Male	123	119
Female	66	68
Age (years)		
Mean (SD)	63.5 (7.6)	62.9 (7.8)
Range	42-79	40-80
Race, n (%)		
White	176 (93.1)	171 (91.4)
Black	1 (0.5)	4 (2.1)
Asian	6 (3.2)	8 (4.3)
Other	6 (3.2)	4 (2.1)
Weight (kg)		
Mean (SD)	75.5 (15.6)	77.2 (16.7)
Range	42.0-117.0	43.5-130.0
Height (cm)		
Mean (SD)	169.1 (9.6)	170.3 (9.0)
Range	146.0-192.0	151.0-194.0
Smoker classification (n)		
Smoker	85	83
Ex smoker	104	104
Duration since diagnosis of COPD (years)		
Mean	6.9	7.4
Median	5.7	5.5
Range	0.5-29.9	0.5-36.5
Trough FEV_1 (L) at Baseline		
Mean	1.3560	1.4900
SD	0.47514	0.49361
Range	0.497-2.923	0.618-2.850
% predicted FEV_1 at Screening		
Mean	53.54	56.62
SD	11.986	12.294
Range	30.9-78.9	30.6-79.1

Baseline is defined as the average of the Visit 2 (Week -1) and pre-dose Visit 3 (Week 0) efficacy spirometry measurements.
For %predicted FEV_1, the Screening value is the post-bronchodilator value from Week -4.
COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; N = number of subjects; n = number of subjects with specified criteria; SD = standard deviation.

Efficacy Results:

Primary Efficacy Endpoint:
Subjects treated with PH-797804 showed an improvement over placebo in mean change from Baseline in trough FEV_1 response after 12 weeks of treatment as summarized in Table 5. At Week 12, there was a greater mean increase from Baseline in trough FEV_1 with PH-797804 (0.0307 L) treatment compared with placebo (0.0048 L) (Table 6). Treatment with PH-797804 achieved 1 of 2 predefined decision criteria in improvement over placebo in

change from Baseline at Week 12 in trough FEV_1. The estimated improvement in trough FEV_1 after 12 weeks was 0.027 L and the corresponding posterior probability of being >0 L was 0.927 (>0.90 required). However, PH-797804 did not meet the second predefined decision criteria of a >0.50 posterior probability of a ≥0.050 L change from Baseline in trough FEV_1 over placebo at Week 12 (estimated posterior probability of 0.104).

Table 5. Trough FEV_1: Treatment Comparison Versus Placebo at Week 12 - FAS

		Difference Between Mean Changes From Baseline (L)	SE	Lower Limit for 1-Sided 90% CI for Difference	C1*	C2a†
Week of treatment comparison versus placebo	n					
Week 12	319	0.027	0.018	0.003	0.927	0.104

* C1: PH-797804 (6 mg) has ≥90% probability of getting >0 L over placebo in change from Baseline trough FEV_1.
† C2a: PH-797804 (6 mg) has ≥50% probability of 0.050 L improvement in FEV_1 and 90% probability of getting >0 mL.
Baseline was defined as the average of the Visit 2 (Week -1) and pre dose Visit 3 (Week 0) efficacy spirometry measurements.
The results include all subjects with at least 1 valid FEV_1 measurement during the active double-blind treatment phase of the study.
The longitudinal mixed effects repeated measures analysis was estimated from mixed model with treatment, week and treatment-by-week interaction fitted as factors and the baseline value as a covariate.
Unplanned readings were excluded from the presentation.
CI = confidence interval; FAS = full analysis set; FEV_1 = forced expiratory volume in 1 second; n = number of subjects with specified criteria; SE = standard error.

Table 6. Trough FEV_1: Mean Baseline and Mean Change From Baseline at Week 12 - FAS

	n	PH-797804 6 mg N=189 Mean (L)	SD	n	Placebo N=187 Mean (L)	SD
Baseline	189	1.3560	0.47514	187	1.4900	0.49361
Mean change From Baseline						
Week 12	153	0.0307	0.16159	166	0.0048	0.16738

Baseline is defined as the average of the Visit 2 (Week -1) and pre-dose Visit 3 (Week 0) efficacy spirometry measurements.
The results include the subjects with at least 1 valid FEV_1 measurement during the active double-blind treatment phase of the study.
Unplanned readings were excluded from the presentation.
FAS = full analysis set; FEV_1 = forced expiratory volume in 1 second; N =number of subjects; n = number of subjects with specified criteria; SD = standard deviation.

Secondary Efficacy Endpoints:

- Improvement in pre-bronchodilator trough FEV_1 was observed for the PH-797804 group over 12 weeks of treatment, compared with placebo; the difference between treatments in

the mean changes from Baseline, averaged over 12 weeks, was 31 mL. Table 7 presents the treatment comparison for mean change from Baseline in trough FEV_1 over 12 weeks.

Table 7. Trough FEV_1: Treatment Comparison Versus Placebo by Week and Treatment Comparison Averaged Over 12 Weeks – FAS

		Difference Between Mean Changes From Baseline (L)	SE	Lower Limit for 1-sided 90% CI for Difference	C1*	C2a†
Week of treatment comparison versus placebo	N					
Week 2	361	0.040	0.015	0.021	0.996	0.244
Week 6	340	0.019	0.017	-0.003	0.870	0.033
Week 10	326	0.039	0.017	0.016	0.986	0.257
Week 12	319	0.027	0.018	0.003	0.927	0.104
Mean change from baseline treatment comparison versus placebo over 12 weeks	361	0.031	0.013	0.014	0.990	0.077

*C1: PH-797804 (6 mg) has ≥90% probability of getting >0 L over placebo in change from Baseline trough FEV_1.
†C2a: PH-797804 (6 mg) has ≥50% probability of 0.050 L improvement in FEV_1 and 90% probability of getting >0 mL.
Baseline is defined as the average of the Visit 2 (Week -1) and predose Visit 3 (Week 0) efficacy spirometry measurements.
The results include the subjects with at least 1 valid FEV_1 measurement during the active double-blind treatment phase of the study.
Unplanned readings were excluded from the presentation.
CI = confidence interval; FAS = full analysis set; FEV_1 = forced expiratory volume in 1 second; n = number of subjects with specified criteria; SD = standard deviation.

- An improvement in trough FEV_6, over placebo, was observed for the PH-797804 group at Week 2 and at Week 10. The difference between treatment means for change from Baseline at Week 2 was 41 mL; the lower limit for the 1-sided 90% CI was 0.0130. The difference at Week 10 was 40 mL; the lower limit for the 1-sided 90% CI was 0.0090. The average mean change from Baseline in trough FEV_6 over 12 weeks was 8 mL for the PH-797804 group and -20 mL for the placebo group; the difference between means was 28 mL.

- An improvement in trough FVC, over placebo, was observed for the PH-797804 group at Week 2 and at Week 10. At Week 2, the mean change from Baseline in trough FVC was 20.3 mL for PH-797804 and -20.9 mL for placebo. At Week 10, the mean change from Baseline was -8.5 mL for PH-797804 and -62.1 mL for placebo. The average change from Baseline over 12 weeks was -9.0 mL for PH-797804 and -42.0 mL for placebo. Table 8 summarizes the differences between the treatments for mean change from Baseline and average over 12 weeks in trough FVC responses at each week.

Table 8. Trough FVC: Treatment Comparison Versus Placebo by Week and Treatment Comparison Averaged Over 12 Weeks- FAS

		Difference Between Mean Changes From Baseline (L)	SE of Difference	Lower Limit for 1-sided 90% CI for Difference
Week of treatment comparison versus placebo	n			
Week 2	361	0.036	0.026	0.0030
Week 6	340	0.024	0.030	-0.0150
Week 10	326	0.056	0.030	0.0180
Week 12	319	0.014	0.031	-0.0260
Mean change from baseline treatment comparison versus placebo over 12 weeks	361	0.033	0.022	0.0040

Baseline is defined as the average of the Visit 2 (Week -1) and predose Visit 3 (Week 0) efficacy spirometry measurements.
The results include all subjects with at least 1 valid FEV_1 measurement during the active double-blind treatment phase of the study.
The longitudinal mixed effects repeated measures analysis was estimated from mixed model with treatment, week and treatment-by-week interaction fitted as factors and the baseline value as a covariate.
Unplanned readings were excluded from the presentation.
CI = confidence interval; FAS = full analysis set; FVC = forced vital capacity; n = number of subjects with specified criteria; SE = standard error.

- There were no differences between the treatments for mean change from Baseline in trough IC responses at any week. The average mean change from Baseline in trough IC over 12 weeks was -8 mL for PH-797804 and -15 mL for placebo with a difference between means of 7 mL.

- There were no differences between the treatment groups in change from Baseline in post-study drug, pre-bronchodilator (ie, post-study drug minus pre study drug) for FEV_1, FEV_6, FVC, and IC at Week 0 and after 12 weeks of therapy.

- There were no differences between the treatment groups in change from Baseline in post-bronchodilator minus pre-bronchodilator FEV_1, FEV_6, FVC, and IC at Week 0 and after 12 weeks of therapy.

- Treatment with PH-797804 showed an improvement in the Mahler Dyspnea Index at Week 2, which continued through Week 12. Mean scores for Mahler TDI Total Focal Score and mean changes from Baseline by week are presented in Table 9. The average change from Baseline over 12 weeks in Mahler TDI Total Focal Score was 1.584 for the PH-797804 group and 1.169 for the placebo group. The difference between the treatments in mean changes from Baseline, averaged over 12 weeks, was 0.415. The comparison between the treatment groups for the mean changes from Baseline in Mahler TDI Total Focal Score, by week, is summarized in Table 10.

Table 9. Mahler TDI Total Focal Score: Mean Baseline and Mean Changes From Baseline by Week - FAS

	n	PH-797804 6 mg N=189 Mean	SD	n	Placebo N=187 Mean	SD
Baseline	186	6.66	1.724	186	6.68	1.753
Mean Change From Baseline						
Week 2	180	1.03	1.957	180	0.88	1.921
Week 6	164	1.58	2.509	175	1.02	2.128
Week 10	156	1.90	2.685	169	1.47	2.263
Week 12	154	2.08	2.634	167	1.46	2.379
Follow-up	183	1.03	2.828	185	0.57	2.830

Baseline is defined as the score at Week 0.
Unplanned readings were excluded from the presentation.
TDI domain scores measure changes from the baseline state of BDI and can range from -3 to +3.
Total (focal) scores were obtained by adding the scores for each of the 3 components for the BDI (range, 0 to 12) and for the TDI (range, -9 to +9).
For any missing components, the total score is scaled up to adjust.
Adjusted total (focal) score = (n/(n-r) × (total focal score) where n = expected number of components, and r = number of missing components.
Results include subjects who had at least 1 valid FEV_1 test during the active double-blinded phase of the study.
BDI = Baseline Dyspnea Index; FAS = full analysis set; N = number of subjects; n = number of subjects with specified criteria; SD = standard deviation; TDI = Transition Dyspnea Index.

Table 10. Mahler TDI Total Focal Score: Treatment Comparisons Versus Placebo by Week - FAS

		Difference Between Mean Changes From Baseline	SE of Difference	Lower limit for 1-sided 90% CI for Difference	C2b*
Week of treatment comparison versus placebo	n				
Week 2	360	0.149	0.20	-0.113	0.7670
Week 6	339	0.506	0.25	0.187	0.9788
Week 10	325	0.427	0.27	0.075	0.9399
Week 12	321	0.577	0.28	0.218	0.9800

* C2b: PH-797804 has ≥90% probability of getting >0 over placebo in BDI/TDI.
Baseline is defined as the score at Week 0.
Unplanned readings were excluded from the presentation.
Total (focal) scores are obtained by adding the scores for each of the 3 components for the BDI (range, 0 to 12) and for the TDI (range, -9 to + 9).
For any missing components, the total score is scaled up to adjust.
Adjusted total (focal) score = (n/(n-r) × (total focal score) where n = expected number of components, and r = number of missing components.
The results include the subjects who had at least 1 valid FEV_1 test during the active double-blinded phase of the study.
The longitudinal mixed effects repeated measures analysis was estimated from mixed model with treatment, week and treatment-by-week interaction fitted as factors, and the baseline value as a covariate.
BDI = baseline dyspnea index; CI = confidence interval; FAS = full analysis set; n = number of subjects with specified criteria; SE = standard error; TDI = transition dyspnea index.

- For change from Baseline in COPD Symptoms as measured by E-RS, the PH-797804 group demonstrated a numerical and statistically significant improvement from Baseline (mean change from Baseline averaged over 12 weeks) for the cough and sputum and for the chest symptoms domains; improvement in change from Baseline for these domains was not significant for the placebo group (Table 11). Treatment comparisons for mean change from Baseline, averaged over 12 weeks, demonstrated a statistically significant difference in favor of PH-797,804 for cough and sputum with a difference between means of -0.200 (upper limit for 1-sided 90% CI for difference = -0.070). There were no significant differences between treatments in mean change from Baseline averaged over 12 weeks for any of the other domains.

Table 11. E-RS Score: Average Change From Baseline Over 12 Weeks - FAS

		PH-797804 (6 mg) (N=188)					Double-Blind Placebo (N=187)				
		n	Mean	SE	90% CI	p-Value	n	Mean	SE	90% CI	p-Value
Breathlessness score	Over 12 weeks	187	-0.008	0.13	(-0.230,0.215)	0.9547	187	-0.076	0.13	(-0.296,0.144)	0.5695
Cough and sputum score	Over 12 weeks	187	-0.244	0.07	(-0.363,-0.126)	0.0008	187	-0.045	0.07	(-0.162,0.073)	0.5316
Chest symptoms score	Over 12 weeks	187	-0.216	0.08	(-0.350,-0.081)	0.0086	187	-0.138	0.08	(-0.272,-0.005)	0.0880
Total score	Over 12 weeks	187	-0.453	0.25	(-0.873,-0.033)	0.0764	187	-0.256	0.25	(-0.673,0.160)	0.3103

Baseline is defined as the average score for the week preceding the start of double-blind treatment (Week 0).
The results include the subjects who had at least 1 valid FEV_1 test during the active double-blinded phase of the study.
Three (3) respiratory symptom domains were embedded in the instrument, breathlessness, cough and sputum, and chest symptoms.
Each domain had been scaled as 0 to 100 scores. Average score of the 7 days is calculated to establish an overall weekly score.
The longitudinal mixed effects repeated measures analysis was estimated from mixed model with treatment, week and treatment-by-week interaction fitted as factors, and the baseline value as a covariate.
CI = confidence interval; FAS = Full Analysis Set; FEV_1= forced expiratory volume in 1 second; N = number of subjects; n = number of subjects with specified criteria; SE = standard error.

- At Week 12, the ratio for the treatments in weekly mean use of a bronchodilator as rescue therapy was 0.974, indicating that subjects receiving PH-797804 required less frequent use of a rescue bronchodilator. Mean use of a rescue bronchodilator, averaged over the 12-week treatment period, is summarized in Table 12. The ratio between the means was 0.963.

Table 12. Rescue Medication Daily E-Diary Entries: Average Over 12 Weeks - FAS

	PH-797804 (6 mg) (N=188)				Double-Blind Placebo (N=187)			
	n	Mean	SE	90% CI	n	Mean	SE	90% CI
Over 12 weeks	186	13.146	0.05	(12.196,14.171)	187	13.650	0.04	(12.692,14.680)

Baseline is defined as the number of puffs of rescue bronchodilator for the week preceding the start of double-blind treatment (Week 0).
The back-transformed results include the subjects who had at least 1 valid FEV_1 test during the active double-blinded phase of the study.
The longitudinal mixed effects repeated measures analysis was estimated for log of number of weekly puffs of rescue bronchodilator from mixed model with treatment, week and treatment-by-week interaction fitted as factors, and the log baseline value as a covariate.
CI = confidence interval; FAS = Full Analysis Set; FEV_1= forced expiratory volume in 1 second; N = number of subjects; n = number of subjects with specified criteria; SE = standard error.

- There were no differences between the treatment groups in changes from Baseline in CRQ-SAS at Weeks 2, 6, 10, and 12. The difference between mean changes from Baseline for the treatment groups was 0.050 at Week 12. The average changes from Baseline over 12 weeks of treatment for the dyspnea domain are summarized in Table 13.

Table 13. CRQ-SAS Dyspnea Score: Average Change From Baseline Over 12 Weeks - FAS

	PH-797804 (6 mg) (N=189)				Double-Blind Placebo (N=187)			
	n	Mean	SE	90% CI	n	Mean	SE	90% CI
Over 12 weeks	168	0.140	0.05	(0.053,0.227)	167	0.132	0.05	(0.047,0.217)

Baseline is defined as the score at Week 0. Unplanned readings have been excluded from the presentation.
Subjects were asked to record their answers on a 7-point scale (1 = maximum impairment to 7 = no impairment).
At least 4 non missing measures are recorded to calculate the average of domain.
The results include the subjects who had at least 1 valid FEV_1 test during the active double-blinded phase of the study.
The longitudinal mixed effects repeated measures analysis was estimated from mixed model with treatment, week and treatment-by-week interaction fitted as factors, and the baseline value as a covariate.
CI = confidence interval; FAS = Full Analysis Set; FEV_1 = forced expiratory volume in 1 second; N = number of subjects; n = number of subjects with specified criteria; SE = standard error.

- The treatment comparison of the subject Global Impression of Change was significant (point estimate >1), in favor of treatment with PH-797804: point estimate = 1.5751, lower limit for the 1-sided 90% Wald CI = 1.2112. The results demonstrated that a greater proportion of subjects taking PH-797804, compared with those taking placebo, rated themselves at the improved end of the Global Impression of Change scale after the 12-week treatment period. The treatment comparison for the physician Global Impression of Change was not statistically significantly different: point estimate = 1.2555, lower limit for 1-sided 90% Wald CI = 0.9653. Results of the

physician and subject Global Impression of Change are provided in Table 14 and Table 15, respectively.

Table 14. Physician Global Impression of Change: Frequency Table of Response at Week 12-FAS

	Very Much Improved n (%)	Much Improved n (%)	Minimally Improved n (%)	No Change n (%)	Minimally Worse n (%)	Much Worse n (%)	Very Much Worse n (%)
PH-797804 (6 mg) (N=154)							
Physician global assessment	5 (3.2)	30 (19.5)	63 (40.9)	50 (32.5)	5 (3.2)	1 (<1.0)	0
Double-Blind Placebo (N=167)							
Physician global assessment	3 (1.8)	31 (18.6)	63 (37.7)	59 (35.3)	11 (6.6)	0	0

The results include the subjects who have at least 1 valid FEV_1 test during the active double-blind phase of the study.
FEV_1 = forced expiratory volume in 1 second; FAS = full analysis set; N = number of subjects; n = number of subjects with specified criteria.

Table 15. Subject Global Impression of Change: Frequency Table of Response at Week 12-FAS

	Very Much Improved n (%)	Much Improved n (%)	Minimally Improved n (%)	No Change n (%)	Minimally Worse n (%)	Much Worse n (%)	Very Much Worse n (%)
PH-797804 (6 mg) (N=154)							
Subject global assessment	6 (3.9)	43 (27.9)	63 (40.9)	37 (24.0)	3 (1.9)	2 (1.3)	0
Double-Blind Placebo (N=167)							
Subject global assessment	9 (5.4)	31 (18.6)	61 (36.5)	56 (33.5)	7 (4.2)	3 (1.8)	0

The results include the subjects who have at least 1 valid FEV_1 test during the active double-blind phase of the study.
FEV_1 = forced expiratory volume in 1 second; FAS = full analysis set; N = number of subject; n = number of subjects with specified criteria.

Safety Results:

AEs: Table 16 summarizes the frequencies of subjects with treatment-emergent AEs.

Table 16. Treatment-Emergent Adverse Events

	PH-797804 6 mg	Placebo
	n (%)	n (%)
Number of subjects	189	187
All causality		
Number of adverse events	249	152
Subjects with adverse events	100 (52.9)	78 (41.7)
Subjects with serious adverse events	9 (4.8)	8 (4.3)
Subjects with severe adverse events	11 (5.8)	8 (4.3)
Subjects discontinued due to adverse events	27 (14.3)	18 (9.6)
Subjects with dose reduced or temporary discontinuation due to adverse events	4 (2.1)	1 (0.5)
Treatment related		
Number of adverse events	65	31
Subjects with adverse events	29 (15.3)	18 (9.6)
Subjects with serious adverse events	1 (0.5)	0 (0.0)
Subjects with severe adverse events	2 (1.1)	2 (1.1)
Subjects discontinued due to adverse events	14 (7.4)	5 (2.7)
Subjects with dose reduced or temporary discontinuation due to adverse events	1 (0.5)	0 (0.0)

Includes all data collected from the first dose of study drug.
Except for the number of adverse events, subjects are counted only once per treatment in each row.
Serious adverse events – according to the Investigator's assessment.
MedDRA (version 15.0) coding dictionary applied.
n = number of subjects; MedDRA = Medical Dictionary for Regulatory Activities.

Table 17 summarizes all-causality treatment-emergent AEs occurring in at least 2 subjects (≥1%) in either treatment group.

Table 17. All-Causality Treatment-Emergent Adverse Events in ≥1% Subjects in any Treatment Group

MedDRA Preferred Term	PH-797804 6 mg N=189	Placebo N=187
	n (%)	n (%)
Lymphadenopathy	0	2 (1.1)
Atrial fibrillation	8 (4.2)	0
Sinus tachycardia	2 (1.1)	1 (0.5)
Vertigo	0	2 (1.1)
Gastresophageal reflux disease	3 (1.6)	0
Nausea	2 (1.1)	0
Diarrhea	5 (2.6)	1 (0.5)
Dyspepsia	3 (1.6)	1 (0.5)
Constipation	3 (1.6)	2 (1.1)
Vomiting	2 (1.1)	2 (1.1)
Toothache	1 (0.5)	2 (1.1)
Dry mouth	0	3 (1.6)
Edema peripheral	2 (1.1)	0
Pyrexia	4 (2.1)	2 (1.1)
Influenza	5 (2.6)	0
Cystitis	2 (1.1)	0
Pneumonia	3 (1.6)	1 (0.5)
Bronchitis	4 (2.1)	2 (1.1)
Oropharyngeal candidiasis	2 (1.1)	1 (0.5)
Upper respiratory tract infection	6 (3.2)	8 (4.3)
Nasopharyngitis	11 (5.8)	15 (8.0)
Sinusitis	1 (0.5)	2 (1.1)
Oral candidiasis	1 (0.5)	3 (1.6)
Pharyngitis	0	3 (1.6)
Contusion	2 (1.1)	0
Hepatic enzyme increased	3 (1.6)	0
Alanine aminotransferase increased	2 (1.1)	0
Aspartate aminotransferase increased	2 (1.1)	0
Blood glucose increased	2 (1.1)	0
Breath sounds abnormal	2 (1.1)	0
Back pain	3 (1.6)	0
Muscle spasms	2 (1.1)	2 (1.1)
Musculoskeletal stiffness	0	2 (1.1)
Myalgia	0	2 (1.1)
Dizziness	4 (2.1)	1 (0.5)
Headache	5 (2.6)	3 (1.6)
Intention tremor	2 (1.1)	0
Insomnia	1 (0.5)	2 (1.1)
Chronic obstructive pulmonary disease	22 (11.6)	21 (11.2)
Cough	2 (1.1)	1 (0.5)
Dysphonia	4 (2.1)	1 (0.5)
Dyspnea	5 (2.6)	0
Epistaxis	2 (1.1)	1 (0.5)
Oropharyngeal pain	2 (1.1)	1 (0.5)
Rhinitis allergic	2 (1.1)	1 (0.5)
Sputum increased	0	2 (1.1)
Upper airway cough syndrome	0	2 (1.1)
Exfoliative rash	3 (1.6)	0
Pruritus	3 (1.6)	3 (1.6)
Rash	11 (5.8)	3 (1.6)
Hypertension	3 (1.6)	3 (1.6)
Deep vein thrombosis	0	2 (1.1)

Table 17. All-Causality Treatment-Emergent Adverse Events in ≥1% Subjects in any Treatment Group

Subjects were counted only once per treatment in each row.
Includes all data collected since the first dose of study drug.
AEs and SAEs are not separated out.
MedDRA (version 15.0) coding dictionary applied.
AEs = adverse events; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects; n = number of subjects with specified criteria; SAEs = serious adverse events.

Treatment-emergent AEs considered by the Investigator as treatment related (Table 18) were reported for 65 subjects in the PH-797804 group and for 31 subjects in the placebo group.

Table 18. Treatment-Emergent Adverse Events (Treatment Related) in ≥1% Subjects in any Treatment Group

MedDRA Preferred Term	PH-797804 6 mg N=189	Placebo N=187
	n (%)	n (%)
Cardiac disorders	3 (1.6)	1 (0.5)
Atrial fibrillation	2 (1.1)	0
Gastrointestinal disorders	11 (5.8)	5 (2.7)
Constipation	2 (1.1)	1 (0.5)
Diarrhoea	2 (1.1)	0
Dry mouth	0	2 (1.1)
Dyspepsia	2 (1.1)	0
Gastrooesophageal reflux disease	2 (1.1)	0
Nausea	2 (1.1)	0
Infections and infestations	2 (1.1)	2 (1.1)
Nasopharyngitis	0	2 (1.1)
Musculoskeletal and connective tissue disorders	2 (1.1)	2 (1.1)
Muscle spasms	2 (1.1)	2 (1.1)
Musculoskeletal stiffness	0	2 (1.1)
Myalgia	0	2 (1.1)
Nervous system disorders	7 (3.7)	4 (2.1)
Dizziness	2 (1.1)	1 (0.5)
Headache	2 (1.1)	2 (1.1)
Intention tremor	2 (1.1)	0
Skin and subcutaneous tissue disorders	14 (7.4)	5 (2.7)
Exfoliative rash	3 (1.6)	0
Pruritus	2 (1.1)	3 (1.6)
Rash	10 (5.3)	2 (1.1)

Subjects were counted only once per treatment in each row.
Includes all data collected since the first dose of study drug.
AEs and SAEs are not separated out.
MedDRA (version 15.0) coding dictionary applied.
AEs = adverse events; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects; n = number of subjects with specified criteria; SAEs = serious adverse events.

Serious Adverse Events (SAEs): Overall, 18 subjects reported a total of 26 SAEs: PH-797804, 10 subjects (4.8%) and placebo, 8 subjects (4.3%). All SAEs are summarized in Table 19.

Table 19. Serious Adverse Events

Serial Number	Serious Adverse Event MedDRA Preferred Term (Verbatim Term)	Causality
PH-797804		
1	Jaundice cholestatic (jaundice cholestatic)	Unrelated
	Pancreatic carcinoma (pancreatic carcinoma)	Unrelated
2	Acute myeloid leukemia (acute myeloblastic leukemia)	Related
3	Demyelinating polyneuropathy (chronic inflammatory demyelinating polyneuropathy)	Unrelated
4	Pneumonia (pneumonia)	Unrelated
5	Disseminated intravascular coagulation (bilateral lobar pneumonia resulting in sepsis, disseminated intravascular bleeding and death)	Related
	Sepsis (bilateral lobar pneumonia resulting in sepsis, disseminated intravascular bleeding and death)	Related
	Lobar pneumonia (bilateral lobar pneumonia resulting in sepsis, disseminated intravascular bleeding and death)	Related
6	Angina unstable (unstable angina pectoris)	Unrelated
7	Patella fracture (patella Fracture); tibia fracture (fractured tibia/fibula plateau); fibula fracture (fractured tibia/fibula plateau)	Unrelated
8	Craniocerbral injury (traumatic brain injury)	Unrelated
	Cerebral hemorrhage (right temporal intracerebral hemorrhage)	Unrelated
	Subdural hematoma (convexity subdural hematoma)	Unrelated
	Syncope (syncopy)	Unrelated
9	Dyspnea (dyspnea of unknown etiology)	Unrelated
10	Atrial fibrillation (paroxysmal atrial fibrillation)	Unrelated
Placebo		
11	Myocardial infarction (myocardial infarct)	Unrelated
12	Chronic obstructive pulmonary disease (COPD exacerbation)	Unrelated
13	Chronic obstructive pulmonary disease (COPD exacerbation)	Unrelated
14	Venous thrombosis (deep venous thrombosis)	Unrelated
	Chronic obstructive pulmonary disease (exacerbation of COPD)	Unrelated
15	Hyponatremia (severe hyponatremia)	Unrelated
16	Vertigo (vertigo)	Unrelated
17	Chronic obstructive pulmonary disease (exacerbation of COPD)	Unrelated
18	Prostate cancer (cancer of prostate)	Unrelated

MedDRA (version 15.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities, COPD = chronic obstructive pulmonary disease, NA = not applicable, SAE = serious adverse event.
a. Onset day is calculated as onset date minus first active therapy date plus 1. Event stop day is calculated as SAE stop date minus first active therapy date plus 1.

Discontinuations: Overall, 27 subjects in the PH-797804 group and 18 subjects in the placebo group discontinued from study drug due to AEs. Table 20 summarizes discontinuations due to AEs.

Table 20. Discontinuations due to Adverse Events

Serial Number	MedDRA Preferred Term	Severity/ Outcome
PH-797804 6 mg		
1	Pancreatic carcinoma	Severe/still present
2	Rash	Moderate/resolved
3	Pneumonia	Severe/resolved
4	Bipolar disorder	Moderate/resolved
5	Intention tremor	Moderate/resolved
6	Chronic obstructive pulmonary disease	Moderate/resolved
7	Lobar pneumonia	Severe/resolved
8	Rash	Mild/resolved
9	Rash	Mild/resolved
10	Rash	Moderate/resolved
11	Angina unstable	Moderate/resolved
12	Hepatic enzyme increased	Moderate/resolved
13	Erysipelas	Moderate/resolved
14	Alanine aminotransferase increased	Mild/resolved
15	Rash	Moderate/resolved
16	Chronic obstructive pulmonary disease	Moderate/resolved
17	Lower limb fracture	Severe/resolved
	Patella fracture	Severe/resolved
18	Atrial fibrillation	Severe/still present
19	Chronic obstructive pulmonary disease	Severe/resolved
20	Craniocerebral injury	Severe/resolved
21	Rash	Moderate/resolved
22	Chronic obstructive pulmonary disease	Moderate/still present
23	Headache	Moderate/resolved
24	Exfoliative rash	Moderate/resolved
25	Chronic obstructive pulmonary disease	Moderate/resolved
26	Atrial fibrillation	Severe/resolved
27	Chronic obstructive pulmonary disease	Moderate/resolved
Placebo		
28	Insomnia	Mild/still present
29	Gastritis	Moderate/resolved
30	Chronic obstructive pulmonary disease	Severe/resolved
31	Chronic obstructive pulmonary disease	Moderate/resolved
32	Myocardial infarction	Moderate/resolved
33	Deep vein thrombosis	Mild/resolved
34	Chronic obstructive pulmonary disease	Moderate/resolved
35	Hyponatremia	Severe/resolved
36	Chronic obstructive pulmonary disease	Moderate/still present
37	Chronic obstructive pulmonary disease	Moderate/still present
38	Chronic obstructive pulmonary disease	Mild/resolved
39	Chronic obstructive pulmonary disease	Moderate/still present
40	Rash	Moderate still present
41	Localized infection	Moderate/resolved
42	Chronic obstructive pulmonary disease	Mild/still present
43	Chronic obstructive pulmonary disease	Moderate/resolved
44	Abdominal pain	Moderate/resolved
45	Chronic obstructive pulmonary disease	Moderate/resolved

MedDRA (version 15.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities.

Dose Reductions or Temporary Discontinuations due to AEs: There were 4 subjects in the PH-797804 group and 1 subject in the placebo group who were temporarily discontinued from study treatment. In the PH-797804 group, 1 subject was temporarily discontinued due to jaundice cholestatic, which was an SAE; the subject was permanently discontinued due to pancreatic carcinoma. One (1) subject temporarily discontinued due to hyperesthesia, which was considered related to study drug; 1 subject temporarily discontinued due to dysphonia; and 1 subject temporarily discontinued due to patella fracture.

In the placebo group, 1 subject temporarily discontinued due to depression.

Deaths: There were 2 deaths reported during this study. One (1) subject died during the treatment period (PH-797,804 group) due to disseminated intravascular coagulation secondary to lobar pneumonia and sepsis. One subject died after completion of the study due to acute myeloid leukemia (death occurred several months after the last dose of PH-797,804).

Laboratory Parameters, Vital Signs and ECG: Few subjects (≤3) had a clinically significant abnormality in any laboratory parameter that was reported as an AE. There were 4 subjects, all in the PH-797804 group, with alanine transaminase values >3 × upper limit of normal (normal range: 6-48 IU/L) during the study. No subject met criteria for Hy's Law. No other significant trends were observed for changes from Baseline or in abnormalities in any of the clinical laboratory parameters.

No marked changes from Baseline in vital signs were observed.

Small mean increases from Baseline (between 7.3 ms and 9.5 ms) were observed in QT corrected for heart rate using Fridericia's formula (QTcF) interval for the PH-797804 group. At Week 12, the mean change from Baseline was 7.6 ms for the PH-797804 group and 0.9 ms for the placebo group. The mean change from Baseline at Follow-up was -0.3 ms for the PH-797804 group and 1.0 ms for the placebo group. No subjects had maximum QTcF intervals ≥500 ms and no subjects had maximum increases from Baseline >60 ms, which were the study specified criteria for discontinuation. There were 3 subjects (2.0%) in the PH-797804 group and 2 subjects (1.2%) in the placebo group with increases from Baseline in QTcF intervals between 30 and <60 ms at Week 12; 0 subjects in the PH-797804 group and 3 subjects (1.8%) in the placebo group had QTcF intervals between 450 and ≤480 ms at Week 12.

CONCLUSIONS:

Primary Endpoint: Treatment with PH-797804 achieved 1 of 2 predefined decision criteria in improvement over placebo in change from Baseline at Week 12 in trough FEV_1. The estimated improvement in trough FEV_1 after 12 weeks was 0.027 L and the corresponding posterior probability of being >0 L was 0.927 (>0.90 required). However, PH-797804 did not meet the second predefined decision criteria of a >0.50 posterior probability of a ≥0.050 L change from Baseline in trough FEV_1 over placebo at Week 12 (estimated posterior probability of 0.104).

Secondary Endpoints:

- Improvement in pre-bronchodilator trough FEV_1 was observed for the PH-797804 group averaged over 12 weeks of treatment. An improvement in trough FEV_6 was observed for the PH-797804 group at Week 2 and at Week 10. An improvement in trough FVC was observed for the PH-797804 group at Week 2 and at Week 10. No statistically significant differences were noted for any other timepoints. There was no apparent change in IC over 12 weeks of treatment.

- There were no differences between the treatment groups in change from Baseline in post-study drug, pre-bronchodilator (post study drug minus pre study drug) for FEV_1, FEV_6, FVC, and IC at Week 0 and after 12 weeks of therapy.

- There were no differences between the treatment groups in change from Baseline in post-bronchodilator minus pre-bronchodilator FEV_1, FEV_6, FVC, and IC at Week 0 and after 12 weeks of therapy.

- Treatment with PH-797804 showed an improvement in the Mahler Dyspnea Index at Week 2 which continued through Week 12.

- For E-RS, there was an improvement for the PH-797804 group in mean change from Baseline averaged over 12 weeks for the cough and sputum and for the chest symptoms domains; improvement in change from Baseline for these domains was not significant for the placebo group. Treatment comparisons for mean change from Baseline, averaged over 12 weeks, demonstrated a statistically significant difference in favor of PH-797804 for cough and sputum. There were no significant differences between treatments in mean change from Baseline averaged over 12 weeks for any of the other domains.

- Subjects receiving PH-797804 required less frequent use of a rescue bronchodilator (per daily diary) over 12 weeks of therapy, compared with placebo, although not statistically significant.

- There were no differences between the treatment groups in changes from Baseline in CRQ-SAS at Weeks 2, 6, 10, and 12.

- The treatment comparison of the subject Global Impression of Change was significant, in favor of treatment with PH-797804, suggesting that a greater proportion of subjects taking PH-797804, compared with placebo, rated themselves at the improved end of the scale after the 12 week treatment period. The treatment comparison for the physician Global Impression of Change was not different.

Safety:

- There were 2 deaths reported for this study: 1 death was reported during the treatment period for a subject in the PH-797804 group who died due to disseminated intravascular coagulation and an additional death was reported after completion of the study for a subject who died due to acute myeloid leukemia. One (1) subject in the PH-797804 group was reported with treatment-related SAEs during the study. Fourteen (14) subjects in the

PH-797804 group and 5 subjects in the placebo group were discontinued due to treatment-related treatment-emergent AEs. Treatment-related severe AEs were reported for 2 subjects in each treatment group.

- Treatment-emergent rash AEs were reported for 15 subjects (18 rash AEs) in the PH-797804 group and for 5 subjects (5 rash AEs) in the placebo group, all of which were either mild or moderate in severity; there were no severe rash AEs reported. All rash AEs reported for the PH-797804 group resolved, with the exception of 1 AE of exfoliative rash; 1 AE of rash reported for the placebo group was still present at the completion of the study. Similar frequencies of treatment-emergent COPD (exacerbation) AEs were reported for the 2 treatment groups: PH-797804, 22 subjects (11.6%) and placebo, 21 subjects (11.2%). Six (6) subjects in the PH-797804 group and 10 subjects in the placebo group were discontinued due to COPD; 1 subject in the PH-797804 group and 2 subjects in the placebo group were severe. Seven (7) subjects in the PH-797804 group compared with no subjects in the placebo group were reported with treatment-emergent atrial fibrillation; 2 subjects were discontinued due to severe atrial fibrillation.

- With the exception of the hepatic enzymes mentioned above no significant trends were observed for changes from Baseline or in abnormalities in any of the clinical laboratory parameters. Few subjects (≤3) had a clinically significant abnormality in any laboratory parameter that was reported as an AE.

- No marked changes from Baseline in vital signs were observed.

- Small mean increases from Baseline were observed in QTcF interval for the PH-797804 group. No subjects had maximum QTcF intervals ≥500 ms and no subjects had maximum increases from Baseline > 60 ms, which were the study specified criteria for discontinuation.

- With the exception of skin, there were no clinically meaningful changes in physical examination findings at last observation compared with Baseline.