

# Efficacy and safety of the oral p38 inhibitor PH-797804 in Chronic Obstructive Pulmonary Disease. A randomized clinical trial

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## Online Data Supplement

### Patient Selection Criteria:

#### Inclusion Criteria

Patients had to meet all of the following inclusion criteria to be eligible for enrolment into the trial :

1. Male or female patients between, and including, the ages of 40 and 80 years. Females had to be of non-childbearing potential. Females of non-child-bearing potential were defined as:
  - Females over the age of 60 years.
  - Females who are 45-60 years of age who have been amenorrhoeic for at least 2 years and have a serum FSH level >30 IU/L in the absence of hormone replacement therapy or have a documented hysterectomy and/or bilateral oophorectomy.
2. Patients with a diagnosis, for at least 6 months, of moderate to severe COPD (GOLD) and who meet the criteria for Stage II-III disease:
  - Patients must have a post-bronchodilator FEV1/FVC ratio < 0.7 and a postbronchodilator FEV1 of 30 - 80% (inclusive) of the predicted value for age, height, race and sex using European Community for Coal and Steel ECCS standards (Luxembourg 1993). To qualify for randomization, these criteria must be met at Screening and replicated during run-in phase (see randomization criteria for details).
3. Patients had to have a smoking history of at least 10 pack-years\* and meet one of the following criteria:
  - They are current smokers or
  - They are ex-smokers who have abstained from smoking for at least 6 months.

\* Formula for pack-years:  
cigarettes = (average number of cigarettes/day ÷ 20) x years of smoking.  
tobacco = ounces per week x 2/7 x years of smoking.
4. Patients must have had stable disease for at least 1 month prior to screening. During the screening and run-in phase patients must be able to manage disease symptoms adequately with short-acting bronchodilators only [i.e. inhaled ipratropium bromide 2 actuations (20µg /actuation) QID administered from a MDI +/- salbutamol (albuterol) rescue medication up to a maximum of 8 actuations (100 µg/actuation) daily], without reliance on other therapies including oral or inhaled corticosteroids, long-acting bronchodilators, nebulizer therapy, theophylline or regular oxygen.
5. Body Mass Index (BMI) < 35 kg/m<sup>2</sup> and a total body weight >40 kg.
6. Patients had to be able to give informed, written consent prior to entering the trial.
7. Patients had to be willing and able to comply with scheduled visit and all trial-related procedures.

#### Exclusion Criteria

1. More than 2 exacerbations of COPD requiring treatment with oral steroids in the preceding year or hospitalization for the treatment of COPD within 3 months of screening or more than twice during the preceding year.

2. History of a lower respiratory tract infection or significant disease instability during the month preceding screening or during the time between screening and randomization.
3. History or presence of respiratory failure, cor pulmonale or right ventricular failure.
4. Patients with home oxygen therapy (either PRN or long-term oxygen therapy, [LTOT]).
5. Any clearly documented history of adult asthma or other chronic respiratory disorders (e.g. bronchiectasis, pulmonary fibrosis, pneumoconiosis).
6. Known previous diagnosis of HIV infection (specific screening is not required).
7. History of cancer (other than cutaneous basal cell) in the previous 5 years.
8. History within the previous 2 years of: myocardial infarction, cardiac arrhythmia (e.g. atrial fibrillation, paroxysmal atrial fibrillation, atrial flutter, supraventricular tachycardia, ventricular tachycardia), left ventricular failure, congestive cardiac failure, unstable angina, coronary angioplasty, coronary artery bypass grafting (CABG) or cerebrovascular accident (including transient ischemic attacks).
9. Tuberculosis without treatment and/or positive tuberculin reaction to PPD (Purified Protein Derivative) without known (documented) vaccination with the bacilli Calmette-Guerin vaccine (BCG).
10. A positive approved immunoassay/ELIA blood test for TB (e.g. TB T-SPOT™, QuantiFERON-Gold test™) where used.
11. History within the previous 6 months of:
  - An epileptic seizure.
  - Poorly controlled Type 1 or Type 2 diabetes.
  - Acute hepatitis of any aetiology.
12. Presenting with:
  - Any condition possibly affecting oral drug absorption (e.g. gastrectomy or clinically significant diabetic gastroenteropathy);
  - Any clinically significant skin lesions as described in Common Terminology Criteria for Adverse Events for Dermatology (CTCAE) Version 3.0;
  - Any clinically significant active infection including herpetic lesions;
  - Congestive heart failure requiring treatment New York Heart Association (NYHA) Class III-IV ;
13. A major surgical operation within 1 month of screening.
14. ECG abnormalities at screening or randomization, including those listed below. The investigator decided whether ECG abnormalities other than those listed were clinically significant and should have excluded the patient from enrolment if abnormality is considered to be clinically significant:
  - Patients with pre-randomization evidence of QTc prolongation at screening or baseline Week 0 (defined as >450 ms) were not eligible for randomization. This assessment was based on a confirmed mean of the triplicate ECG recordings and was made by the investigator at the time of ECG collection.
  - Predominant heart rhythm other than normal sinus rhythm e.g. atrial fibrillation, atrial flutter, supraventricular tachycardia.
  - Atrioventricular (AV) block greater than first degree.
  - Resting heart rate >100 or <40 bpm.
  - Evidence of previous myocardial infarction in the absence of clinical history consistent with these findings.
  - Evidence of acute ischaemia.

15. History or evidence, based upon a complete medical history, full physical examination, posterior-anterior chest X-ray (within last 12 months), 12-lead resting ECG or clinical laboratory test results, of any other significant concomitant clinical disease that, in the opinion of the investigator, could interfere with the conduct, safety or interpretation of results of this trial. Patients with certain chronic conditions such as hypertension, thyroid disease, Type 1 or Type 2 diabetes, hypercholesterolemia, gastroesophageal reflux, or depression could be included in the trial providing the conditions were well controlled and medications prescribed to treat the condition were not prohibited, had been stable for the month prior to screening and would not be predicted to compromise safety or interfere with the tests and interpretations of this trial.
16. Evidence of organ dysfunction or hematopoietic disorder based on any of the following assessments:
  - Hgb <10 g/dL, Hct <32%;
  - Absolute WBC count <3.0 x 10<sup>9</sup>/L (<3000/mm<sup>3</sup>)
  - Neutrophil count < 1.2 x 10<sup>9</sup>/L (<1200/ mm<sup>3</sup>)
  - Platelet count <100 x 10<sup>9</sup>/L (<100,000/ mm<sup>3</sup>)
  - AST or ALT >1.2 x ULN
  - Total bilirubin >1.2 x ULN
  - Alkaline phosphatase >1.2 x ULN
  - Albumin <3.5 g/dL or 35 g/L due to known liver disease
  - Serum creatinine >ULN
17. Positive HBsAg, HBcAb or anti-hepatitis C virus serology.
18. Use of any of the prohibited concomitant medications within the time frame prior to the start of screening or during the run-in period.
19. Use of any investigational drug within 1 month, or 5 half lives, prior to screening whichever was longer.
20. History of severe drug induced hypersensitivity (i.e. anaphylaxis).
21. Contraindication for rescue/maintenance medication i.e. salbutamol (albuterol) or ipratropium bromide.
22. Donation of, or intent to donate blood, or blood components for one month prior to the trial, during the trial or within 1 month after completion of the trial.
23. Evidence of alcohol or drug abuse or dependency (specific screening is not required).
24. Inability to comprehend, or unwillingness to follow, the trial requirements including attendance at out-patient clinic visits and participation in laboratory testing as called for by the protocol.

## Analytical Methodology

hsCRP was measured using a validated immunoturbidimetric assay (Quintiles), CC16 was measured using an enzyme-linked immune-sorbent assay (ELISA) kit (CC16 ELISA, DiaMed Eurogen) which was cross-validated to a previously validated assay with a different kit (Human Clara Cell Protein ELISA, BioVendor). Fibrinogen and SPD were measured by ELISA using commercial kits (Ref No. HFIBKT, Patricell Ltd, and RD194059100, BioVendor) and IL-6 was measured by Luminex, fluorescence (Human IL-6 Singleplex Bead Kit, Ref No. LHC0061, Invitrogen).

## Statistical Methodology Details

The analysis of the primary endpoint in this study used Bayesian statistics. This approach has advantages over a classical hypothesis testing approach as a) direct probabilistic statements of the effect size in this trial could be made (not addressed by p-values) and b) information on the placebo-response could be borrowed from previous trials, reducing the number of placebo patients required. The Bayesian estimation of the dose-response also means that sample size is reduced over paired testing as information is borrowed from neighboring doses

Secondary endpoints were analyzed using a classical repeated measures analysis of covariance approach using SAS. The longitudinal mixed-effects model fitted baseline, treatment, week and treatment by week as fixed effects terms in the model. Patient was to be fitted as a random effect, and the covariance structure across time points was to be estimated from the data (i.e. an unstructured covariance matrix). One-sided testing was utilized as it was not of interest to continue development if there was no difference or the difference was worse than placebo.

To model the dose-response a Bayesian three-parameter  $E_{\max}$  model, was originally planned, however this model did not provide an appropriate fit to the data. This was largely driven by a smaller mean improvement in trough  $FEV_1$  in the 10-mg dose group at Week 6 compared with the 3 and 6-mg groups, hence the Week 6 analysis used the pre-specified alternative normal dynamic linear model (NDLM) (E1). This model essentially fits a Bayesian spline to the data. The results presented are based on non-informative priors.

The NDLM estimate was adjusted for baseline and 95% Credible Intervals (CrI) of the effect size were presented together with the direct posterior probabilities of each dose having an effect over placebo greater than 0 mL and 75 mL. A Bayesian CrI informs the reader that there is 95% chance that the true effect lies in the interval.

Numerous other models were fitted as part of the sensitivity analysis and irrespective of model fitted, there was strong evidence that PH-797804 had a positive effect on lung function in this trial.

## References:

- E1 Smith MK, Jones I, Morris MF, Grieve AP, Tan K. Implementation of a Bayesian adaptive design in a proof of concept study. *Pharm Stat* 2006; 5: 39–50.