# Effect of Once-Daily Fluticasone Furoate/Vilanterol on 24-Hour Pulmonary Function in Patients With Chronic Obstructive Pulmonary Disease: A Randomized, Three-Way, Incomplete Block, Crossover Study

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## ABSTRACT

**Background:** Available inhaled corticosteroid/long-acting $\beta_2$-agonist combinations for chronic obstructive pulmonary disease (COPD) require twice-daily administration. The combination of fluticasone furoate (FF) and vilanterol (VI) FF/VI is being developed in a novel dry powder inhaler for the treatment of COPD and asthma with the potential for once-daily dosing. Results from Phase II studies have shown clinically and statistically significant improvements over placebo in trough (24-hour postdose) forced expiratory volume in 1 second ($FEV_1$) after once-daily dosing with FF or VI (VI concurrently with an inhaled corticosteroid) in asthma and VI in COPD.

**Objectives:** This Phase III, multicenter, randomized, double-blind, placebo-controlled study was designed based on guidance from drug regulators with the goal of evaluating the 24-hour spirometric effect of once-daily FF/VI in patients with COPD.

**Methods:** Patients (aged ≥40 years) who completed a 2-week placebo run-in period were randomized to 1 of 18 three-course sequences of placebo and 2 of 3 dose combinations of FF/VI (50/25 μg, 100/25 μg, and 200/25 μg), dosed once daily in the morning. Each 28-day treatment period was separated by a 2-week, single-blind, placebo washout period. The primary end point was time-adjusted (weighted mean) 0 to 24-hour $FEV_1$ (AUC) at the end of each 28-day treatment period (period days 28–29). Safety profile assessments included incidence of adverse events (AEs) (defined according to the Medical Dictionary for Regulatory Activities), 12-lead ECG outputs, vital signs (pulse rate, diastolic and systolic blood pressure) and clinical laboratory assessments (including fasting serum glucose and potassium) and 24-hour serum cortisol. The pharmacokinetics of FF and VI were assessed at the end of each 28-day treatment period with FF/VI.

**Results:** Eighty-seven patients were screened; 54 completed run-in and were randomized to double-blind treatment. The mean patient age was 57.9 years, and 46% were male. The majority of patients were current smokers (83%) and were receiving short-acting $\beta_2$-agonists within the 3 months before screening (63%). All 3 strengths of once-daily FF/VI demonstrated significantly higher 0 to 24-hour (period days 28–29) change from period baseline weighted mean $FEV_1$ than placebo: adjusted mean improvements from placebo in $FEV_1$ for FF/VI were 220 to 236 mL (all, $P < 0.001$). Improvements versus placebo in change from period baseline serial $FEV_1$ measures were observed at each time-point and with each strength of FF/VI over the 0 to 25-hour period (period days 28–29), indicating sustained bronchodilation. The overall incidence of on-treatment AEs was low (10%–12% with FF/VI; 4% with placebo); 2 serious AEs were reported during washout periods (1 AE after FF/VI 50/25 μg and 1 AE after placebo) but neither was considered treatment related. No serious AEs were reported during the treatment periods or during the

For information regarding institution names, please see the table in **Supplemental Appendix C** in the online version at http://dx.doi.org/10.1016/j.clinthera.2012.06.005.

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follow-up period. No clinically or statistically significant differences from placebo were reported for serum glucose or potassium. No significant effects on vital signs, ECG, or 24-hour serial serum cortisol were reported. The extent of systemic exposure to FF and VI at steady state was low for all strengths of FF/VI.

**Conclusions:** FF/VI inhaled once daily in the morning for 28 days produced significant improvements in pulmonary function with a prolonged (>24 hours') duration of action in this population of patients with COPD. The combination was well tolerated. ClinicalTrials.gov identifier: NCT01072149. (*Clin Ther*. 2012;34:1655–1666)


**Key words:** COPD, fluticasone furoate, efficacy, once-daily, vilanterol.

## INTRODUCTION

Combination pharmacologic therapies in chronic obstructive pulmonary disease (COPD) consisting of a long-acting $\beta_2$-agonist (LABA) plus an inhaled corticosteroid (ICS) are more effective than the individual components in modifying disease progression through positive effects on lung function, symptoms, and prevention of exacerbations.[1–9]

Currently available ICS/LABA combinations for COPD require twice-daily administration. Once-daily treatment has the potential to improve adherence and simplify treatment in chronic diseases such as COPD.[10] Longer-acting component drugs are being investigated with the aim of developing new once-daily inhaled combination treatments.

Vilanterol (VI) is an inhaled LABA with 24-hour activity.[11] Fluticasone furoate (FF) is an enhanced-affinity ICS with a pharmacologic profile that demonstrates greater retention in the lung and longer duration of action than fluticasone propionate (FP).[12,13] The combination FF/VI is being developed in a single, multidose, novel dry powder inhaler with the potential for once-daily dosing.

This is the first study to evaluate the 24-hour spirometric effect of different doses of FF added to VI (FF/VI 50/25 μg, 100/25 μg, and 200/25 μg) after 28 days of once-daily treatment in patients with COPD.

## PATIENTS AND METHODS

This Phase III, multicenter, randomized, double-blind, placebo-controlled, 3-way, incomplete block, crossover study of 3 dose combinations of FF/VI in patients with COPD was conducted at 8 centers in the United States between January 27, 2010, and July 1, 2010 (study code HZC110946).

### Patients

Eligible patients (aged ≥40 years) had a documented clinical history of COPD[14]; a post-bronchodilator forced expiratory volume in 1 second ($FEV_1$) of ≤70% predicted and a $FEV_1$/forced vital capacity ratio of ≤0.70[15]; a current habit or history of ≥10 pack-years of cigarette smoking; and a score of ≥2 (on a scale of 1–4) on the Modified Medical Research Council Dyspnea Scale.[16] Key exclusion criteria are provided in the **Supplemental Appendix A** in the online version at http://dx.doi.org/10.1016/j.clinthera.2012.06.005. The method used to collect spirometry readings during the study is described in **Supplemental Appendix B** in the online version at http://dx.doi.org/10.1016/j.clinthera.2012.06.005.

All patients gave written informed consent before their screening visit. Patients could be compensated for their participation in the study. If a center compensated patients, this was stated clearly in standardized text on the consent form. The study was approved by local ethics review committees (for further details see **Supplemental Appendix C** in the online version at http://dx.doi.org/10.1016/j.clinthera.2012.06.005) and was conducted in accordance with the Declaration of Helsinki[17] and Good Clinical Practice Guideline.[18]

### Study Design and Treatments

Patients who completed the 2-week placebo run-in period were randomized to 1 of 18 three-course sequences of placebo and 2 of 3 dose combinations of FF/VI (50/25 μg, 100/25 μg, or 200/25 μg). The central randomization schedule was generated by the sponsor by using a validated computerized system (RandALL). Patients were randomized to treatment by using an automated, telephone-based Registration and Medication Ordering System (RAMOS). Each treatment was inhaled once a day in the morning for 28 days using a novel dry powder inhaler. Neither the patient nor the study investigator knew which study medication the patient was receiving. All inhaler devices were identical. Study medication taken during the washout periods was single blind (patient blinded to the treatment they were receiving). Treatment periods were separated by 2-week, single-blind, placebo washout periods, and a safety follow-up visit was conducted 7 days after the last treatment day. Patients attended