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# Assessment of the efficacy and safety of fluticasone propionate and salmeterol delivered as a combination dry powder via a capsule-based inhaler versus a multi-dose inhaler in patients with chronic obstructive pulmonary disease

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ABSTRACT

*Background:* This study tested the clinical non-inferiority of the fluticasone propionate/salmeterol combination 50/250 μg (FSC) Rotacaps®/Rotahaler® system, a single unit dose inhaler, with the multi-dose FSC Diskus® inhaler in adults with chronic obstructive pulmonary disease (COPD).

*Methods:* This multi-centre, randomised, double-blind, double-dummy, two-way cross-over study compared 12 weeks' treatment of FSC administered twice daily using Rotacaps/Rotahaler or Diskus. The primary endpoint was change from baseline in trough morning forced expiratory volume in 1 s ($FEV_1$) at Day 85, and the pre-defined non-inferiority criteria was: the lower limit of the confidence interval (CI) for the treatment difference (Rotacaps/Rotahaler-Diskus) in least squares (LS) mean change from baseline, being greater than −45 mL. Secondary endpoints included change in breathlessness (as measured by transition dyspnoea index (TDI)) and COPD-specific health status measures.

*Results:* The LS mean increase from baseline in trough $FEV_1$ at Day 85 was 116 mL in the Rotacaps/Rotahaler group and 91 mL in the Diskus group (difference in model-adjusted LS mean change: 25 mL (95% CI 2 mL, 47 mL)), the lower limit of the CI for the treatment difference being greater than the protocol-defined criterion for non-inferiority i.e. −45 mL. Data for breathlessness, COPD-specific health status and safety parameters were similar following FSC treatment via either inhaler.

*Conclusions:* This study demonstrated the clinical non-inferiority of FSC 50/250 μg when administered using Rotacaps/Rotahaler compared with Diskus in patients with COPD. The risk:benefit profile for the two inhalers was comparable.



## 1. Introduction

Chronic obstructive pulmonary disease (COPD) is an inflammatory disease characterized by persistent and progressive airflow limitation. Whilst COPD is preventable and treatable, it represents a major public health challenge across developed and developing countries, largely attributable to the continued exposure to risk factors (tobacco and biomass fuels) and an ageing population [1,2]. By 2030, COPD is projected to be the fourth leading cause of death and the seventh leading cause of disability-adjusted life years (DALYs) worldwide [2]. Patients from countries with lower social economic status (SES) have been reported to have worse COPD outcomes (morbidity and mortality) than those from countries with higher SES [3]. This is partly associated with less accessible healthcare including access to affordable inhaled COPD therapies [4,5].

Effective pharmacological therapy can reduce COPD symptoms and the frequency of exacerbations, as well as improve health status and exercise tolerance [1]. Inhaled bronchodilator therapies are central to the management of COPD symptoms and combination therapy with inhaled corticosteroids and long-acting $beta_2$-agonists (ICS/LABA) have demonstrated greater efficacy than ICS alone in improving lung function, health status and exacerbation frequency [1,6]. Fluticasone propionate and salmeterol

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combination product (FSC) is approved for the treatment of COPD and is currently available in metered dose inhaler (MDI) and multi-dose powder inhaler (Diskus®) devices. The Rotacap®/Rotahaler® system is a single unit dose inhaler currently licensed with salbutamol in a number of markets for the treatment of asthma and COPD. An FSC Rotacap/Rotahaler has been developed as an alternative treatment option to a monthly multi-dose inhaler. Such an option could potentially improve the access to inhaled COPD therapies in developing countries by facilitating the more frequent purchase of smaller units of FSC versus the comparatively expensive up-front cost of a multi-dose inhaler.

The aim of the current study was to establish the clinical non-inferiority of FSC 50/250 μg Rotacap/Rotahaler compared with FSC 50/250 μg Diskus in adults with COPD.

## 2. Methods

### 2.1. Study design and patients

This was a multi-centre, randomised, double-blind, double-dummy, two-way cross-over study conducted at 52 centres in four countries, Argentina (12 centres), Mexico (9 centres), Russian Federation (14 centres), and Ukraine (17 centres), between November 2013 and April 2015 (GSK protocol 115646; NCT01978145) (Fig. 1).

Following a 3-week run-in period, eligible patients were randomised to receive initial active treatment with either FSC 50/250 μg Rotacap/Rotahaler or FSC 50/250 μg Diskus. In each 12-week treatment period patients took one inhalation from the Diskus followed by one from the Rotahaler twice daily (one active treatment and one placebo), morning and evening. There was 4-week washout between treatments. Study treatment was assigned from a centralized, computer-generated schedule (RandAll [GlaxoSmithKline, UK]) using an interactive voice response system. All patients received training to ensure correct inhaler technique and attended 4 weekly clinic visits to be assessed. Compliance was monitored during the study by counting the number of returned Rotacap capsules and via the dose counter on the Diskus. If a patient was non-compliant (took <80% or >120% of study treatment within a treatment period), the patient was re-educated on the correct use of the study treatment. During run-in and wash-out periods, all patients were treated with salbutamol 200mcg BID by DISKUS as maintenance therapy. Rescue medication (salbutamol 100mcg MDI) that was locally sourced was provided for symptomatic relief and allowed throughout the entire study period.

The study included male or female patients aged 40–80 years with a diagnosis of COPD in accordance with the American Thoracic Society/European Respiratory Society definition [7] who at baseline had a measured pre- and post-salbutamol/albuterol forced expiratory volume in 1 s ($FEV_1$)/forced vital capacity (FVC) ratio of <0.70, a pre-salbutamol/albuterol $FEV_1$ <50% of predicted, a post-salbutamol/albuterol $FEV_1$ ≥30% of predicted, and a score of ≥2 on the Modified Medical Research Council Dyspnoea Scale (mMRC). Included patients were required to have a current or prior history of at least 10 pack-years of cigarette smoking.

Patients who experienced a COPD exacerbation or lower respiratory tract infection (requiring the use of antibiotics, systemic corticosteroids, or hospitalisation); or pneumonia (presumptive diagnosis or radiographically confirmed) during the study were withdrawn. Full details of the study criteria, permitted and prohibited medications and study withdrawal criteria can be found in the online supplement.

Prior to participation, all patients gave their written informed consent. The study was reviewed and approved by relevant ethics committee/institutional review boards and regulatory authorities.

### 2.2. Study outcomes

#### 2.2.1. Efficacy

The primary efficacy endpoint was the change from baseline in trough morning $FEV_1$ at the end of each treatment period (Day 85). Secondary endpoints were serial $FEV_1$ (summarised as area under the curve over 10 h [$AUC_{0\text{-}10}$]) and the change from baseline in: trough $FEV_1$ at Day 28 and 56, Transition Dyspnoea Index (TDI) [8], and change from baseline St George's Respiratory Questionnaire (SGRQ) total score measured using the COPD specific SGRQ-C [9] and COPD Assessment Test (CAT) score [10].

Trough $FEV_1$ was measured electronically by spirometer in the morning before the use of bronchodilator and morning study medication dosing (and within 10–16 h after previous evening dose), and after completion of breathlessness and health status questionnaires. Patients were asked to withhold their rescue medication for at least 6 h and theophylline for at least 12 h before testing. On Day 85 of treatment, serial $FEV_1$ measurements were taken at pre-dose, 15 min, 30 min, and 1, 2, 4, 6, and 10 h post morning dosing.

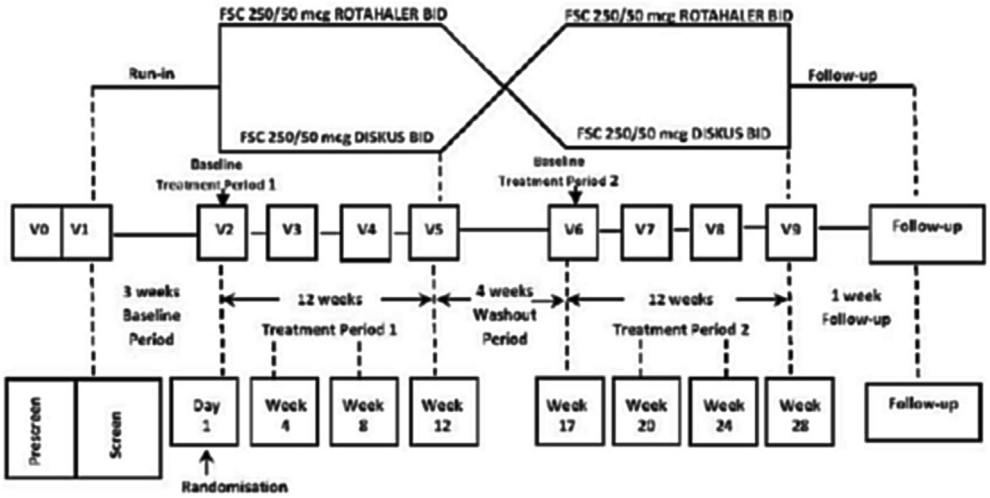


**Fig. 1.** Study design. FSC: fluticasone propionate/salmeterol combination.