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Clinical trial paper

Randomised, double-blind, placebo-controlled, cross-over single dose study of the bronchodilator duration of action of combination fluticasone furoate/vilanterol inhaler in adult asthma

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ABSTRACT

Background: Fluticasone furoate (FF)/vilanterol (VI) is a once-daily maintenance treatment for asthma and chronic obstructive pulmonary disease. The duration of bronchodilation beyond 24 h has not been determined previously.

Methods: Adults aged 18–65 (n = 32), with asthma and reversibility to salbutamol (≥15% and ≥200 mL increase in forced expiratory volume in 1 s [FEV_1]) participated in a double-blind, placebo-controlled, crossover study. Patients were admitted to a clinical trials unit for 72 h, and inhaled, in random order, placebo or FF/VI 100/25 mcg via ELLIPTA dry powder inhaler on two occasions 7–14 days apart. FEV_1 was measured at baseline, 15 and 30 min, 1, 2, 4, 12, 24, 36, 48, 60, and 72 h. The differences in change in FEV_1 from baseline between treatments and corresponding two-sided 95% confidence intervals (CI) were calculated at each time point.

Findings: FF/VI produced a rapid onset of bronchodilation (adjusted mean difference in change from baseline in FEV_1 versus placebo at 15 min, 252 mL [95% CI 182–322]). Maximum bronchodilation was observed at 12 h (adjusted mean difference in the change from baseline in FEV_1, 383 mL [95% CI 285–481]). Bronchodilation was maintained throughout the 72-h assessment period (adjusted mean difference in the change in FEV_1 from baseline at 72 h, 108 mL (95% CI 15–200]). FF/VI was well tolerated and no serious side effects were reported.

Interpretation: A single dose of FF/VI 100/25 mcg showed evidence of a 72-h bronchodilator duration of action in adults with asthma.

1. Introduction

International asthma guidelines recommend the use of combination inhaled corticosteroid (ICS)/long-acting β_2 agonist (LABA) therapy as the preferred maintenance treatment in moderate to severe asthma [1]. However, current ICS/LABA products require twice-daily dosing and treatment adherence represents a potential problem [2–5]. This has led to the development of the next generation of inhaled LABA and corticosteroid medications with a longer duration of action to enable once-daily dosing, with the potential to improve patient convenience and enhance compliance [4–6].

Vilanterol trifenatate (VI) is a member of the next generation of LABAs with at least a 24-h duration of bronchodilator action [7–10]. *In-vitro* studies have shown it to be more potent and to have greater intrinsic activity than salmeterol, with a similar selectivity profile for the β_2-adrenoceptor (AR) over both the β_1-and β_3-AR subtypes compared with salbutamol, and superior to the other β-agonists

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tested [7]. In human airways, VI has a faster onset and longer duration of action than salmeterol, exhibiting significant bronchodilation 22 h after treatment [7]. Fluticasone furoate (FF) is a novel glucocorticoid that has enhanced affinity for the glucocorticoid receptor, with fast association and slow dissociation [11]. These properties result in a longer duration of action and prolonged retention in the lung, compared with fluticasone propionate (FP), and have enabled its use as a once-daily medication in asthma [12–15].

The combination FF/VI inhaler (Relvar/Breo ELLIPTA®; ELLIPTA® is a trademark of the GSK group of companies) is efficacious as a once-daily treatment in asthma [16–18] and COPD [19–23]. The bronchodilator effects of FF/VI are well characterised up to 24 h in patients with asthma [17,18] and COPD [19,21–23]. However, there is still significant bronchodilation at 24 h [17–23] and persistence of bronchodilation beyond this dosing interval time point has not been determined. The aim of this study was to investigate the duration of the bronchodilator effect over a 72-h period following a single dose of the combination FF/VI 100/25 mcg inhaler administered in the morning in adult patients with asthma. The secondary objective was to investigate the onset of bronchodilation.

2. Methods

2.1. Patients

Volunteers for this study were recruited from the Medical Research Institute of New Zealand database of asthma volunteers and local newspaper advertising. The first patient was screened in October 2013 and the last patient completed the study in September 2014. Adults aged 18–65 years with a diagnosis of asthma by a doctor were eligible for inclusion if at screening they demonstrated a pre-bronchodilator predicted forced expiratory volume in 1 s (FEV_1) ≥60%, an increase ≥15% over baseline and an absolute change of ≥200 mL within 30 min following four inhalations of salbutamol 100 mcg via metered dose inhaler through a spacer device. Patients were required to be on an ICS for at least 12 weeks prior to screening and be clinically stable on a daily dose of ICS (FP 100–500 mcg or equivalent), with or without a short-acting β2-agonist (SABA) for 4 weeks prior to the screening visit. Patients were also required to be able to replace their current asthma treatments with a SABA inhaler from 7 days prior to randomisation until study completion and withhold their SABA for at least 6 h prior to study visits. Important exclusion criteria included a history of life-threatening asthma, current smoker or a pack year history of ≥10 years, other significant pulmonary diseases, respiratory infection within 1 month of entry to the study, any asthma exacerbation that required oral corticosteroids or that resulted in hospitalisation within 12 weeks of screening, LABA use in the 12 weeks prior to screening, or a significant electrocardiograph abnormality. More detailed inclusion and exclusion criteria can be found in a summary of the protocol at http://www.gsk-clinicalstudyregister.com/study/116592?study_ids=116592#ps.

2.2. Study design

This was a randomised, double-blind, placebo-controlled, cross-over study (Clinicaltrials.gov ID: NCT01837316; Supplementary Fig. S1). Patients were admitted to the Clinical Trials Unit (CTU) at Wellington Regional Hospital for 72 h on two occasions to receive the randomised treatments, FF/VI 100/25 mcg inhalation powder administered via the ELLIPTA dry powder inhaler (DPI) and placebo (first strip lactose, second strip lactose, and magnesium stearate) administered via the ELLIPTA DPI.

Within 21 days of the screening visit, eligible patients attended on Day 1 of the treatment period. Spirometry was undertaken at baseline (pre-medication) and then at 15 and 30 min, 1, 2, 4, 12, 24, 36, 48, 60, and 72 h post-medication administration. Spirometry was performed using a body plethysmograph (Masterscreen Body, Erich-Jaeger, Friedberg, Germany). The highest value of three technically acceptable manoeuvres was retained as per American Thoracic Society/European Respiratory Society guidelines [24]. Between 7 and 14 days later, patients returned to the clinic for treatment period 2 and the procedures were repeated with whichever study medication they had not already received (Supplementary Fig. S1). Patients attended again within 10 days for a final follow-up assessment.

Maintenance ICS was stopped 24 h prior to study medication dosing until 72 h after dosing. Smoking and caffeine or xanthine-containing products were forbidden for 8 h prior to the study medication administration until completion of the 72-h assessments.

Patients were required to avoid SABA use as a rescue medication for 8 h prior to screening. Patients were also requested to avoid SABA use during the 72-h study periods in the CTU unless absolutely necessary and, if possible, not within 8 h of the next lung function assessment. SABA use was recorded, and if used within 8 h prior to any lung function assessment, the data from that time point were excluded from the analysis.

2.3. Randomisation and masking

Patients were assigned to one of two treatment sequences (AB or BA, where A was placebo and B was FF/VI 100/25 mcg) in accordance with the randomisation schedule, which was generated by the study statistician prior to the start of the study, using validated internal software. The investigators and patients were blinded to the treatment assignments.

2.4. Sample size

The sample size was based on feasibility, with some justification derived from a previous study in this subject population, in which the standard deviation (SD) of the paired difference in FEV_1 between a combination ICS/LABA medication and placebo was 190 mL [25]. This was used to obtain an estimate of within subject SD to assess the width of the confidence interval (CI) for the difference between treatments based on the proposed sample size of 32 patients. Based on the within patient SD of 270 mL and a sample size of 32 patients, this equates to a half width of a 95% CI of 138 mL. This calculation is based on a symmetric two-tailed procedure and a type I error rate of 5%.

2.5. Statistical methods

The primary objective of the study was to estimate the bronchodilator effect over 72 h following a single dose of FF/VI 100/25 mcg compared with placebo. Changes from baseline in FEV_1 at time points 15, 30 min, 1, 2, 4, 12, 24, 36, 48, 60, and 72 h post dose were the main endpoints. Baseline was defined as Day 1 pre-dose measurement for FEV_1 for each treatment period. A mixed effects repeated measures analysis of covariance model was fitted, with fixed effect terms for treatment, period, time, time by treatment interaction, patient baseline, period baseline, sex, and age fitted as covariates, with subject as a random effect. From these analyses, point estimates and their associated 95% CIs were constructed for each treatment at each time point and the difference between adjusted means and the corresponding two-sided 95% CI was calculated at each time point. In a post-hoc assessment, the adjusted mean change in FEV_1 from baseline following FF/VI, and