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The efficacy of once-daily fluticasone furoate/vilanterol in asthma is comparable with morning or evening dosing

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Summary
Aim: To investigate the effect of time of day of dosing (morning or evening) on lung function following administration of fluticasone furoate (FF)/vilanterol (VI) 100/25 mcg.
Methods: Double-blind, placebo-controlled, randomised, three-way crossover study. Subjects with persistent asthma ($N = 26$) received FF/VI (morning or evening) or matching placebo once-daily for 14 (±2 days) via dry powder inhaler (DPI). Weighted mean (0–24h) and pre-treatment FEV_1 (morning and evening) were determined after the Day 14 evening dose, together with mean pre-treatment (morning and evening) peak expiratory flow (PEF) on Days 2–12.
Results: FF/VI 100/25 administered morning or evening produced clinically significant increases in weighted mean FEV_1: the differences [95% confidence interval (CI)] from placebo were 377 mL [293, 462] and 422 mL [337, 507], respectively; the difference between morning and evening dosing was −44 mL [−125, 36]. Day 14 pre-treatment morning FEV_1 differences [95% CI] from placebo were 403 mL [272, 533] and 496 mL [369, 624] after morning and evening dosing, respectively; the morning:evening treatment difference was −94 mL [−221, 34]. Pre-treatment evening FEV_1 differences [95% CI] from placebo were 275 mL [169, 380] and 309 mL [205, 413] after morning and evening dosing, respectively; the morning:evening treatment difference was −34 mL [−138, 70]. FF/VI (morning or evening) produced rapid increases in PEF with the full

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effect apparent after the first dose and maintained throughout the 14-day treatment period.
Conclusion: FF/VI 100/25 produces comparable improvements in lung function whether dosed in the morning or evening in subjects with persistent asthma.
[GSK protocol HZA114624, NCT01287065].

Introduction

International guidelines advocate the use of an inhaled corticosteroid combined with a long-acting beta-agonist (ICS/LABA) for the maintenance therapy of asthma patients who remain symptomatic despite use of low-medium dose ICS alone [1,2]. Currently available ICS/LABA treatments (fluticasone propionate (FP)/salmeterol, budesonide/formoterol and mometasone furoate/formoterol) are administered twice daily [3—5]. Simplifying the dosing regimen to once daily, particularly for chronic conditions such as asthma may improve compliance and disease management, providing sustained 24-h bronchodilation and bronchoprotection [6—9].

Fluticasone Furoate/Vilanterol (FF/VI) Inhalation Powder is a once-daily ICS/LABA combination for the treatment of asthma and COPD. When delivered via a dry powder inhaler (DPI), FF/VI has demonstrated a good safety and tolerability profile with improvements in lung function in asthma [10—12] and COPD patients [13,14].

Considerable evidence exists to support the concept that asthma is influenced by circadian rhythms, with symptoms worsening and lung function decreasing at night [15—19]. Given this chronobiology of asthma, it is not surprising that time of administration has been shown to influence the efficacy of some bronchodilators with once-daily dosing in the evening potentially being the most effective treatment paradigm [15,18—21]. These time dependent effects of corticosteroid administration have been seen in asthma with evening dosing proving the most effective time for some once-daily ICS formulations with respect to lung function and reduction of side-effects relating to cortisol suppression [22—25]. Previous data have shown once-daily evening dosing with FF 400 mcg to be as effective as twice-daily dosing with FF 200 mcg [22] and therefore, FF/VI has been dosed in the evening across the Phase II and Phase III asthma development programme [10—12]. Individual patients may prefer to choose what time of day they take their medication. Therefore, having the flexibility of dosing either in the morning or evening may be more convenient for the patient and may further improve treatment adherence and the management of asthma symptoms.

The potential effects of altering the time of day of dosing of FF/VI have not been previously explored. Therefore, the current study directly compared the effect of morning and evening dosing of FF/VI 100/25 mcg on lung function over 24 h in subjects with persistent bronchial asthma. FF/VI 100/25 contains the optimal dose of each component for patients uncontrolled on low-medium dose ICS and will probably be the most widely used clinical dose.

Methods

Subjects

Healthy non-smokers (i.e. not smoked within past 12 months; pack history $\leq$10 pack years), aged 18—70 years (inclusive) with a body mass index (BMI) within range 19.0—29.9 kg/m^2 were included. Females were of non-childbearing potential (i.e. post-menopausal or surgically sterile) or using protocol-specified contraception. Subjects had a documented history of persistent asthma treated with an ICS with or without a short-acting beta-agonist (SABA) for at least 12 weeks prior to screening, a best pre-bronchodilator FEV_1 $\geq$60% predicted, (predicted values were based on NHANES III) [26] and reversibility FEV_1 $\geq$12% over baseline and absolute change $\geq$200 mL (10—30 min after a SABA). Subjects were clinically stable on an ICS dose (fluticasone propionate [FP] at 100—250 mcg twice-daily [total daily dose 200—500 mcg] or equivalent ICS) within the 4 weeks preceding screening. Subjects with significant abnormalities in the 12-lead electrocardiogram (ECG), vital signs or clinical laboratory assessments at screening were excluded. Subjects were excluded if they had any asthma exacerbation requiring oral corticosteroids within 12 weeks or hospitalisation within 6 months prior to screening or they had taken high doses of ICS (FP $>$ 250 mcg twice-daily [total daily dose $>$500 mcg FP or equivalent]) within 8 weeks of screening or oral steroids within 12 weeks of screening or they had an unresolved respiratory infection within 4 weeks before screening which led to a change in asthma management or status.

Study design

This was a randomised, double-blind, placebo-controlled, three-way crossover study conducted between October 2010 and September 2011 at a single site (P3 Research Ltd, New Zealand). The study was conducted in accordance with the Declaration of Helsinki and approved by an independent ethics committee prior to the start of the study. Informed consent was obtained prior to any study procedures. A study schematic is provided in Fig. 1. Subjects received three different treatments administered by oral inhalation via DPI and were dosed twice daily to maintain the blind (Table 1). FF/VI doses or placebo were administered at approximately 09:00 and 21:00. Dosing started with the evening dose on Day 1. Subjects were dosed for 14 $\pm$ 2 days i.e. the timing of Day 14 was flexible and could take place within $\pm$2 days of the actual Day 14 time point. The 24-h assessment period started at the evening dosing time