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Efficacy and safety of fluticasone furoate 100 µg once-daily in patients with persistent asthma: A 24-week placebo and active-controlled randomised trial[☆]

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Summary

Inhaled corticosteroids (ICSs) improve asthma disease control; once-daily ICS administration may have advantages for patients. Our objective was to assess the efficacy and safety of the novel ICS fluticasone furoate (FF) over 24 weeks versus placebo.

This was a 24-week double-blind, double-dummy, placebo- and active-controlled study (NCT01159912) of 343 asthma patients (≥12 years) not controlled by their current ICS. Patients were randomised (1:1:1) to FF100 µg, placebo (both administered once-daily [OD] via

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ELLIPTA™ dry powder inhaler in the evening) or fluticasone propionate (FP) 250 µg (administered twice-daily (BD) via DISKUS™/ACCUHALER™). Primary endpoint was change from baseline in pre-dose evening forced expiratory volume in 1s (FEV₁) at Week 24; change from baseline in % rescue-free 24-h periods was a powered secondary endpoint. Adverse events (AEs) were assessed.

FF100 µg OD and FP250 µg BD significantly improved pre-dose evening FEV₁ compared with placebo at Week 24 (+146 ml [$p = 0.009$] and +145 ml [$p = 0.011$], respectively). Percentage of rescue-free 24-h periods was increased with FF100 µg OD (+14.8%) and FP250 µg BD (+17.9%) compared to placebo (both $p < 0.001$). On-treatment AEs were reported by 53% (FF100 µg OD), 42% (FP250 µg BD) and 40% (placebo) of patients. On-treatment severe asthma exacerbations were lower with FF100 µg OD (3%) and FP250 µg BD (2%) than placebo (7%). There was significant suppression of urinary cortisol at week 24 with FF100 µg OD ($p = 0.030$) and FP250 µg BD ($p = 0.036$) relative to placebo.

FF100 µg OD, administered in the evening, achieves significant improvements in lung function and rescue inhaler use over 24 weeks, comparable to FP250 µg BD with similar safety profile.

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Introduction

Inhaled corticosteroids (ICS) are the cornerstone of therapy for all severities of persistent asthma, with benefits including control of asthma symptoms, improvements in lung function and a decrease in airway hyper-responsiveness [1]. However, there continues to be potential to improve disease control in adults and children, especially from the perspective of adherence which, when low, can contribute to poor asthma control [1–3].

Fluticasone furoate (FF) is a novel ICS in development for once-daily (OD) use in asthma. Structurally, FF is distinct from the twice-daily (BD) ICS, fluticasone propionate (FP) [4]. Preclinically, FF exhibits a greater anti-inflammatory activity than FP [5,6]. Clinically, FF, administered once-daily in the evening is non-inferior to the same daily dose administered twice daily with respect to lung function [7]; exhibits significant effects versus placebo with respect to lung function over a range of doses and asthma severities [8–10]; has shown a significant effect on the allergen-induced early asthmatic response 23–24 h after dosing [11]; and is indicated as a once-daily therapy for allergic rhinitis [12,13].

Dose-ranging studies of FF performed over 8 weeks have shown that the 100 µg dose provides a significant benefit in asthma [8,9], and exhibits similar lung function effects to FP250 µg BD in patients uncontrolled by low-dose ICS alone [9]. The present study sought to determine further whether this dose of FF (hereafter referred to as FF100 µg OD), given once-daily in the evening, is effective and tolerable over a longer period in patients with asthma uncontrolled by their current ICS. The primary endpoint was the effect of FF100 µg OD on lung function measured approximately 24-h post-dose at Week 24; secondary endpoints included symptomatic assessments of asthma, and safety was also assessed. The study was placebo-controlled and included FP250 µg BD as a reference arm for internal validation of results; it was not designed to assess non-inferiority or equivalence of FF100 µg OD to FP250 µg BD. Some of the results from this study have been presented in abstract form [14].

Methods

Patients

Patients were required to be ≥ 12 years of age with a diagnosis of asthma [15] for ≥ 12 weeks and maintained on a stable dose of ICS for ≥ 4 weeks prior to the screening visit. A pre-bronchodilator forced expiratory volume in 1s (FEV₁) of 40–90% predicted, adjusted for ethnicity [16], and evening reversibility of $\geq 12\%$ and ≥ 200 ml following albuterol/salbutamol inhalation were also required. Patients were required to be current non-smokers (≥ 3 months) with a smoking history of less than 10 pack-years. Long-acting beta₂ agonists were not permitted within 4 weeks of the screening visit. The study was approved by local ethics review committees and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent from each adult (≥ 18 years) patient was obtained prior to performing any study-specific procedures, as was assent and written parental consent for each adolescent (12–17 years) patient.

Study design

This was a 24-week, randomised, multicentre, placebo- and active-controlled, double-blind, double-dummy, parallel-group study (GSK study FFA112059; [ClinicalTrials.gov](http://dx.doi.org/10.1016/j.jrmed.2013.11.009) NCT01159912) conducted at 56 centres in five countries between 30 June 2010 and 16 January 2012. Eligible patients entered a 4-week run-in period during which they were maintained on their stable dose of ICS (long-acting beta₂ agonists were not permitted), switched their rescue short-acting beta₂ agonist (SABA) to albuterol/salbutamol, and recorded symptoms, rescue use and morning/evening peak expiratory flow (PEF) in an electronic daily diary. Patients were eligible for randomisation if at the end of the 4-week run-in period they were (i) uncontrolled on their stable dose of run-in ICS medication, i.e. exhibited an evening pre-dose FEV₁ 40–90% of predicted and reported an asthma symptoms score of ≥ 1 and/or rescue use on 4 of

the last 7 days of the run-in period; and (ii) compliant with baseline medication and daily diary completion on 4 of the last 7 days of the run-in period.

The central randomisation schedule was generated by the sponsor using a validated computerised system (RandAll). Subjects were randomised using the Registration and Medication Ordering System (RAMOS), which was used by the study investigators or their designees to register and randomise the patients and receive their medication assignment information. Patients were randomised 1:1:1 to receive placebo, FF100 µg OD or FP250 µg BD. FF100 µg OD was administered in the evening (5 pm–11 pm) via the ELLIPTA™ dry powder inhaler (DPI) (representing an emitted dose of 92 µg) (ELLIPTA™ is a trademark of the GlaxoSmithKline group of companies). Evening dosing for FF was employed based on prior studies which indicated once-daily evening dosing is as efficacious as the same daily dose given twice daily, compared to once-daily morning dosing where a numerical advantage was observed with the same daily dose given twice daily [17]. FP250 µg BD was administered in the morning and evening via the DISKUS™/ACCUHALER™ device. Placebo was administered once-daily in the evening via the ELLIPTA DPI or twice daily via the DISKUS/ACCUHALER as appropriate. To maintain the study blind each patient received an ELLIPTA DPI (from which they inhaled once-daily in the evening) and a DISKUS/ACCUHALER (from which they inhaled twice daily). Study visits took place at Weeks 2, 4, 8, 12, 16, 20 and 24; follow-up contact was conducted up to 1 week after completing study medication.

Assessments

The primary endpoint was mean change from baseline in pre-dose evening FEV₁ at 24 weeks. FEV₁ was measured electronically by spirometry at 5–11 pm using standard techniques. The mean change from baseline in the percentage of rescue-free 24-h periods over the 24 weeks of the study was a powered secondary endpoint. Additional secondary endpoints comprised mean change over the study period from baseline in evening/morning PEF and percentage of symptom-free 24-h periods. Change from baseline in the Asthma Quality of Life Questionnaire for 12 years and older (AQLQ+12; Qoltech, Bosham, UK) score at weeks 12 and 24 was also a secondary endpoint. Other endpoints were the change from baseline in the Asthma Control Test™ (ACT: QualityMetric, Inc. Lincoln, RI, USA) score at weeks 12 and 24, and withdrawal due to lack of efficacy. The AQLQ+12 and ACT were administered at baseline and Study Visits 6 and 9 (Weeks 12 and 24).

Safety endpoints comprised the incidence of adverse events (AEs) and serious AEs (SAEs). Asthma exacerbations, defined as the need for oral or systemic corticosteroids for ≥3 days, or any hospitalisation requiring oral or systemic corticosteroids, and worsening of asthma, defined as the need for treatment additional to study medication and rescue medication were also assessed (but not specified as safety endpoints); as was pneumonia (confirmed by chest X-ray) and oral/oropharyngeal candidiasis (assessed by oropharyngeal examination at each study visit and recorded as an AE if present). Standard laboratory parameters (haematology, clinical chemistry) and vital signs were

assessed at baseline, 24 h-urine cortisol (UC) excretion was assessed at baseline and study end.

Statistical analysis

The primary comparison of interest was the difference between FF100 µg OD and placebo, while FP250 µg BD was also compared to placebo. The primary endpoint was pre-dose evening FEV₁ at Week 24 using last observation carried forward. This was assessed by analysis of covariance. The majority of the powered secondary, secondary and other endpoint comparisons were analysed using the same approach. AQLQ+12 and ACT were analysed using a repeated measures model and withdrawals due to lack of efficacy were analysed using Fisher's Exact test. To account for multiplicity across key endpoints a step-down closed testing procedure was employed (see additional methods in [Online Supplementary Material](#)). No formal analysis of differences between FF100 µg OD and FP250 µg BD was planned prior to the study; however the relative effects of FF100 µg OD and FP250 µg BD could be assessed by comparison of point estimates for FF100 µg OD versus placebo comparisons, and whether they lay within the 95% confidence interval for point estimates of FP250 µg BD versus placebo comparisons.

Additional detailed methods are provided in the [Online Supplementary Material](#).

Results

Study population

Of 1036 patients screened, 349 were randomised, resulting in an intention-to-treat (ITT) population of 343, of whom 255 completed the study ([Fig. 1](#)). The most common reason for early withdrawal was lack of efficacy which included asthma exacerbations, most of which occurred in the placebo group. Demographic and patient baseline characteristics are shown in [Table 1](#). The majority of study patients were white (79%) or of African heritage/African-American (19%), the mean (standard deviation [SD]) duration of asthma was 18.28 (14.006) years. ICSs most frequently used during prior to screening and during run-in were FP (42–48%) or budesonide (26–29%).

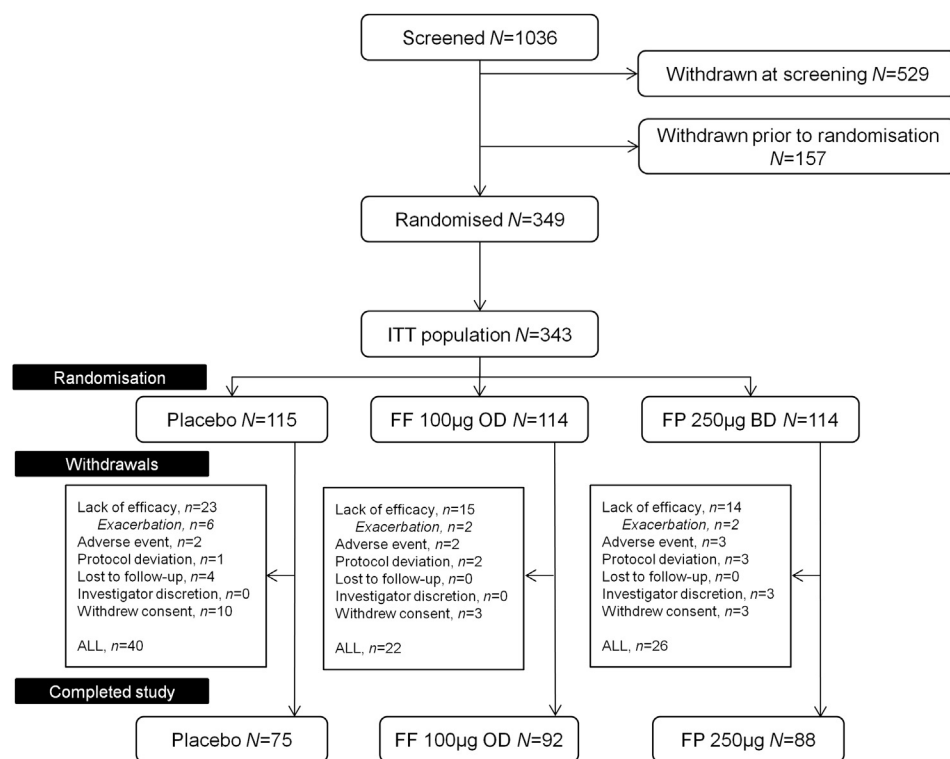
Efficacy

Primary endpoint

Pre-dose evening FEV₁ was significantly improved at Week 24 relative to placebo by both FF100 µg OD and FP250 µg BD; both active treatments resulted in similar effects compared with placebo ([Table 2](#)). Results for the PP population replicated those for the ITT population ([Online Supplementary Material, Table 1](#)). Over the study a small increase in pre-dose evening FEV₁ was observed in the placebo-treated group but both FF100 µg OD and FP250 µg BD caused greater effects ([Fig. 2/ Online Supplementary Material, Fig. 1](#)).

Powered and other secondary endpoints

The percentage of rescue-free 24-h periods was significantly increased compared with placebo for both FF100 µg



Note: one patient was not randomised but received treatment (placebo) in error. Six patients were randomised in error but did not receive study treatment. These seven patients are not included in the ITT population.

Figure 1 Patient disposition. BD, twice daily; FF, fluticasone furoate; FP, fluticasone propionate; ITT, intention-to-treat; OD, once-daily.

OD and FP250 µg BD (Table 2). In a *post-hoc* sensitivity analysis no difference from placebo was observed for change from baseline in evening PEF with FF100 µg OD (Table 2). The rationale for the *post-hoc* sensitivity analysis and time-course figures for evening and morning PEF are provided in the [Online Supplementary Material \(Additional Methods and Fig. 2\)](#). Initial analysis of evening PEF found no significant difference between placebo and active therapy ([Online Supplementary Material Table 2](#)) meaning significance (regardless of *p*-value) could not be inferred for all subsequent efficacy comparisons because of the step-down closed testing procedure employed. Morning PEF, percentage of symptom-free 24-h periods over the course

of the study and AQLQ+12 at Weeks 12 and 24 were numerically improved by both active treatments compared with placebo (Table 2). Least squares (LS) mean changes from baseline in the AQLQ+12 at week 24 were +0.51, +0.84 and +0.68 units in the placebo, FF100 µg OD and FP250 µg BD arms, respectively.

Other outcomes

Improvements from baseline ACT score were observed for both active treatments compared with placebo at weeks 12 and 24 (Table 2). LS mean changes from baseline were +2.5 in the placebo arm, +3.9 in the FF100 µg OD arm and +3.6

Table 1 Baseline characteristics (intention-to-treat population).

	Placebo N = 115	FF100 µg OD N = 114	FP250 µg BD N = 114
Age (years), mean (SD)	40.3 (17.68)	40.1 (16.17)	41.4 (15.64)
Female sex, n (%)	68 (59)	63 (55)	72 (63)
Pre-bronchodilator FEV ₁ (l) mean (SD)	2.326 (0.6493)	2.374 (0.6285)	2.364 (0.7256)
Predicted baseline FEV ₁ (%) mean (SD)	72.32 (10.871)	72.18 (10.387)	73.04 (11.936)
Reversibility (%) mean (SD)	25.43 (12.959)	27.32 (15.252)	25.07 (14.537)
Symptom-free 24-h periods (%) mean (SD)	3.9 (10.58)	7.9 (20.45)	7.0 (20.99)
Rescue-free 24-h periods (%) mean (SD)	18.5 (29.19)	13.3 (24.52)	17.1 (30.49)
AQLQ+12, mean (SD)	4.95 (0.971)	4.81 (1.132)	4.76 (1.040)
Asthma Control Test, mean (SD)	15.9 (3.23)	15.4 (3.77)	15.4 (3.53)
Asthma Control Test <20, n (%)	100 (87)	98 (86)	100 (88)

AQLQ+12, Asthma Quality of Life Questionnaire for 12 years and older; BD, twice daily; FEV₁, forced expiratory volume in 1s; FF, fluticasone furoate; FP, fluticasone propionate; OD, once-daily; SD, standard deviation.

Table 2 Treatment differences between active therapy and placebo for primary and secondary endpoints (intention-to-treat population).

	FF100 µg OD vs. placebo	FP250 µg BD vs. placebo
Pre-dose evening FEV ₁ (l): difference in LS mean change from baseline (95% CI) at week 24 (LOCF)	0.146 (0.036, 0.257) <i>p</i> = 0.009	0.145 (0.033, 0.257) <i>p</i> = 0.011
Rescue-free 24-h periods (%): difference in LS mean change from baseline (95% CI) over weeks 1–24	14.8 (6.9, 22.7) <i>p</i> < 0.001	17.9 (10.0, 25.7) <i>p</i> < 0.001
Evening PEF (l/min): difference in LS mean change from baseline (95% CI) over weeks 1–24 ^a	5.8 (–1.9, 13.6) <i>p</i> = 0.141	8.3 (0.6, 16.1) <i>p</i> = 0.036
Morning PEF (l/min): difference in LS mean change from baseline (95% CI) over weeks 1–24 ^a	11.0 (3.4, 18.7) –	6.6 (–1.1, 14.2) –
Symptom-free 24-h periods (%): difference in LS mean change from baseline (95% CI) over weeks 1–24	8.9 (1.1, 16.7) –	8.8 (1.1, 16.6) –
AQLQ+12 (units): difference in LS mean change from baseline (95% CI) at week 12	0.24 (0.03, 0.45) –	0.28 (0.07, 0.49) –
AQLQ+12 (units): difference in LS mean change from baseline (95% CI) at week 24	0.33 (0.09, 0.57) –	0.16 (–0.08, 0.41) –
Asthma Control Test (units): difference in LS mean change from baseline (95% CI) at week 12	1.8 (0.8, 2.7) –	1.6 (0.6, 2.5) –
Asthma Control Test (units): difference in LS mean change from baseline (95% CI) at week 24	1.4 (0.4, 2.5) –	1.1 (0.1, 2.1) –

AQLQ+12, Asthma Quality of Life Questionnaire for 12 years and older; BD, twice daily; CI, confidence interval; FEV₁, forced expiratory volume in 1s; FF, fluticasone furoate; FP, fluticasone propionate; LOCF, last observation carried forward; LS, least squares; OD, once-daily; PEF, peak expiratory flow; SD, standard deviation.

^a *Post-hoc* sensitivity analysis; initial analysis results and rationale for sensitivity analysis presented online; *p*-values are not indicated for endpoint comparisons below evening PEF in the testing hierarchy due to the closed step-down approach employed.

in the FP250 µg BD arm. At baseline 13%, 14% and 12% of patients exhibited an ACT score of ≥ 20 , indicating well-controlled asthma, in the placebo, FF100 µg OD and FP250 µg BD groups respectively. At Week 24 the corresponding percentages of patients with ACT score ≥ 20 were 48%, 55% and 51%, respectively. Twenty percent of patients withdrew due to lack of efficacy with placebo treatment. For FF100 µg OD and FP250 µg BD 13% and 12% of patients withdrew for the same reason, respectively. As illustrated in [Online Supplementary Material Fig. 3](#), both active

treatments resulted in lower withdrawal rates compared with placebo.

Safety

A greater number of AEs, drug-related AEs and on-treatment AEs was observed with FF100 µg OD therapy compared with FP250 µg BD or placebo; no difference was apparent in the number of patients experiencing AEs leading to withdrawal ([Table 3](#)). Drug-related AEs in ≥ 2 patients are listed in ([Online Supplementary Material Table 3](#)). On-treatment candidiasis (oral or oropharyngeal) occurred more frequently with FF100 µg OD (*n* = 6) than with FP250 µg BD (*n* = 2) or placebo (*n* = 0). A total of nine on-treatment or post-treatment SAEs were reported in seven patients. Pyelonephritis and meningitis were reported by one patient each with placebo treatment. Abscess, Crohn's disease and epididymal cyst were reported by one patient each with FF100 µg OD treatment; one further patient receiving FF100 µg OD reported prostate cancer, *Escherichia* bacteraemia and pyelonephritis. Supraventricular tachycardia was reported by one patient receiving FP250 µg BD. The occurrence of Crohn's disease was the only SAE that led to withdrawal; none of the SAEs were considered to be related to the study drug. No deaths (asthma-related or otherwise) occurred during the study, nor did any asthma-related hospitalisations.

Severe on-treatment asthma exacerbations occurred in three (3%) patients receiving FF100 µg OD, two (2%) receiving FP250 µg BD and eight (7%) receiving placebo. All of these events were managed with systemic/oral corticosteroids. The least squares (LS) mean ratio to baseline at

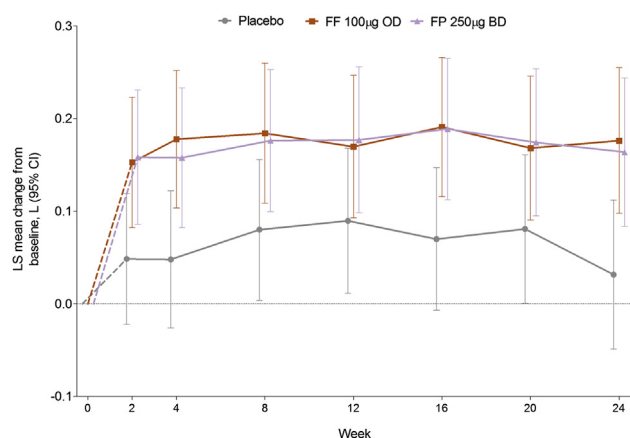


Figure 2 Repeated measures analysis of change from baseline in pre-dose evening FEV₁ over 24 weeks (intention-to-treat population). BD, twice daily; CI, confidence interval; FEV₁, forced expiratory volume in 1s; FF, fluticasone furoate; FP, fluticasone propionate; LS, least squares; OD, once-daily.

Table 3 Summary of AEs (intention-to-treat population).

n (%)	Placebo N = 115	FF100 µg OD N = 114	FP250 µg BD N = 114
On-treatment AEs	46 (40)	60 (53)	48 (42)
Drug-related AEs ^{a,b}	7 (6)	11 (10)	7 (6)
AEs leading to withdrawal ^b	2 (2)	3 (3)	3 (3)
On-treatment SAEs	2 (2)	4 (4)	1 (<1)
Drug-related SAEs	0	0	0
SAEs leading to withdrawal	0	1 (<1)	0
On-treatment AEs occurring in ≥5% of patients			
Bronchitis	7 (6)	8 (7)	4 (4)
Headache	5 (4)	7 (6)	7 (6)
Nasopharyngitis	6 (5)	9 (8)	4 (4)
Upper respiratory tract infection	6 (5)	7 (6)	6 (5)

AE, adverse event; BD, twice daily; FF, fluticasone furoate; FP, fluticasone propionate; OD, once-daily; SAE, serious adverse event.

^a As deemed by the investigator.

^b On-treatment and post-treatment.

week 24 for LS geometric mean 24-h UC was 1.15 for placebo, 0.88 for FF100 µg OD and 0.88 for FP250 µg BD (UC population; [Supplementary Online Material Fig. 4](#)). Analysis of these ratios indicated significant differences between placebo and FF100 µg OD (0.76 [95% confidence interval {CI}: 0.60, 0.97] $p = 0.030$) and between placebo and FP250 µg BD (0.77 [95% CI 0.60, 0.98] $p = 0.036$). No difference was apparent between FF100 µg OD and FP250 BD.

Discussion

The principal findings of this study were that (i) FF100 µg OD dosed in the evening over 24 weeks significantly improved lung function (pre-dose evening FEV₁) relative to placebo; (ii) the effect observed on lung function seen with FF100 µg OD was similar to that observed with FP250 µg BD; (iii) improvements in pre-dose evening FEV₁ with FF100 µg OD and FP250 µg BD were observed at the first time point assessed (Week 2), and were maintained throughout the study period; (iv) the percentage of 24-h periods free from the use of rescue medication was significantly improved with both FF100 µg OD and FP250 µg BD compared with placebo; and (v) a higher incidence of AEs was observed with FF100 µg OD compared to FP250 µg BD or placebo, though no difference was seen in the number of patients with AEs leading to withdrawal, and no SAEs were considered related to study medication.

Clinical decision-making in asthma is guided by the concept of asthma control [1] which is based on the frequency of symptoms and rescue use, the limitation of activities and pre-bronchodilator lung function; this approach has been prospectively assessed, with the majority of, but not all, patients studied achieving asthma control with an ICS or ICS/long-acting beta₂ agonist combination [18]. In

the present study FF100 µg OD resulted in significant effects on both pre-dose evening FEV₁ and the percentage of rescue 24-h periods, compared with placebo; both of these endpoints are elemental components of the assessment of asthma control. That the effects seen on these endpoints with FF100 µg OD were similar to those achieved with FP250 µg BD suggests similar efficacy between the two therapies. Our study cohort was well matched across treatment groups and indicated that patients were using rescue medication most days at baseline and exhibited an FEV₁ that was approximately 72–73% of predicted, despite the use of a stable dose of ICS prior to study entry; i.e. at baseline the population was uncontrolled. This was also reflected by the majority of patients exhibiting an ACT score of ≤20 at baseline and a mean baseline ACT score of 15.4 in both active treatment arms and 15.9 in the placebo arm. Despite this level of uncontrolled asthma both FF100 µg OD and FP250 µg BD exhibited numerically greater effects than placebo on ACT, percentage of symptom-free 24-h periods and quality of life. However, it should be noted that while the minimally important difference (MID) for a change in ACT of 3 units [19] was not achieved versus placebo for either active therapy, the percentage of patients achieving well-controlled asthma (i.e. ACT ≥20) was greater in the ICS treatment groups than in those on placebo at the end of the 24-week treatment period, and the change from baseline did reach the MID with both active therapies but not with placebo. Equally, while the MID of 0.5 points [20] was not achieved for the AQLQ+12 versus placebo for either active therapy it was achieved versus baseline in both active treatment arms. The observation that the MID for the AQLQ+12 was also achieved in the placebo arm (+0.51 units) may have been due to a healthy survivor effect, as more patients withdrew from the placebo arm than the FF100 µg OD or FP250 µg BD arms. These findings suggest that the effects of FF100 µg OD and FP250 µg BD on lung function, rescue use and symptom-free 24-h periods translated to a trend for improvement in the perception of symptoms and quality of life, albeit one that was not clinically important relative to placebo. Although statistical inference cannot be drawn from these comparisons it is apparent that the overall trend for effect suggests that FF100 µg OD has a positive effect on all of the key criteria related to the modern management of asthma. The findings with the active control (FP250 µg BD) suggest the study population was responding as expected to an established ICS; that the magnitude of the differences observed between FF100 µg OD and placebo, and FP250 µg OD and placebo were similar suggests the two ICS treatments had similar therapeutic effects.

The 100 µg dose of FF has previously been shown to improve pre-dose evening FEV₁ relative to placebo in asthma patients uncontrolled by a SABA alone [8] or uncontrolled on a low-dose ICS [9] over a period of 8 weeks. This improvement, though numerically lower in our study compared with the prior studies [8,9] was still statistically significant and was maintained for the 6-month duration of the study. The lower magnitude of effect observed in the present study possibly reflects differences in study design, patient cohort as determined by inclusion criteria, or other differences. It is important to note that the difference for FP250 µg BD versus placebo in our study was also lower than

that recorded in previous studies of FP in asthma [21]. Improvements in lung function with ICS treatment vary greatly in different patients and studies [21], making it difficult to compare across studies. Furthermore, the overall level of asthma control in the Western world has increased over the last 20 years [22]; these observations may also have contributed to the effects observed here with FF100 µg OD and FP250 µg BD.

An important difference between the two active treatments, from a patients' perspective, is once- versus twice-daily dosing. Studies in a number of diseases, including cardiovascular disease [23] and hypertension [24], have shown that adherence to medication is increased with an OD versus a BD treatment regimen. Similar findings have been reported in asthma [25,26]. While an association between adherence and asthma control is known [27] the question remains as to whether OD dosing results in an increase in adherence in a 'real-world' setting, and whether any increase in adherence translates to an increase in asthma control.

Similar percentages (~40%) of patients reported AEs with placebo or FP250 µg BD treatment, while AEs with FF100 µg OD were reported by an additional ~10% of patients. This increase in the total number of AEs reported with FF100 µg OD was primarily caused by a greater prevalence of rare events reported by one or two patients in the FF100 µg OD compared with the FP250 µg BD and placebo groups; i.e. no novel AE signal was observed with FF100 µg OD. A small but significant reduction in urinary cortisol was observed after 24 weeks of treatment with both FF100 µg OD and FP250 µg BD, an observation that has been reported in a 4-week study of FF100 µg/FF200 µg OD [7] and in a 12-week study of FF100 µg combined with the OD long-acting beta₂ agonist vilanterol [28]. However, these findings contrast with those of previous studies of FF100 µg OD assessed over 8-weeks [8,9,17] or 12-weeks [28], or with FF100 µg/FF200 µg OD combined with vilanterol over 24 weeks [29,30] or 52 weeks [31]. Serum cortisol is a more sensitive and reliable measure of cortisol secretion than urine sampling and in a 6-week study involving complete 24-h serum cortisol profiling (with 0–24 h weighted mean serum cortisol as the primary endpoint), FF/VI 100/25 mcg and FF/VI 200/25 mcg OD did not suppress serum cortisol (treatment ratio [95% CI] to placebo: 0.99 (0.87, 1.12) and 0.97 (0.86, 1.10), respectively) [32]. Corticosteroids, inhaled or otherwise, have the potential to induce adrenal suppression particularly when used at high doses, for a long duration, or by children [33–35]. The balance of evidence from studies of up to 52 weeks in duration, including the serum cortisol findings, suggests that clinical doses of FF (or FF/vilanterol) are unlikely to induce clinically relevant reductions in urinary cortisol, but further longer-term studies are warranted to assess any potential effect on cortisol levels in susceptible patients.

The current study included patients with asthma uncontrolled by their current ICS (who were therefore representative of the patient population in which FF100 µg OD may be used), was of sufficient duration to determine longer-term benefits and adverse events, and was both placebo- and active-controlled. The step-down closed statistical testing procedure employed represents both a strength and a limitation. This approach is a rigorous means

of accounting for multiplicity of comparisons. In this study it meant, consequently, that no significance could be inferred for comparisons of morning and evening PEF, symptoms, quality of life and measures of asthma control. Another limitation of this study is that it was not powered or designed to analyse non-inferiority of FF100 µg OD and FP250 µg BD. Furthermore, even though many asthma patients are smokers [36] these individuals were excluded, to avoid any overlap with chronic obstructive pulmonary disease and chronic bronchitis, as is typical of most asthma clinical trials. This is relevant, as smoking is known to have a detrimental effect on the response to ICS in asthma patients [37,38] and the efficacy and safety of FF in asthma patients who smoke remains to be determined. Finally, the <1 year study duration, and which only covered part of the Winter/Spring seasons when respiratory viruses are a major cause of asthmatic exacerbations, could be a possible limitation but exacerbation frequency was not a focus of this study (it was a safety endpoint).

In conclusion, this study shows that FF100 µg OD in asthma patients not controlled by their current ICS therapy significantly improves pre-dose evening FEV₁ and rescue use to an extent that is similar to that provided by FP250 µg BD, and is well tolerated.

Conflicts of interest

JL has served as a consultant to and received lecture fees from AstraZeneca, GlaxoSmithKline, Merck Sharpe and Dohme, Novartis and UCB Pharma; has been partly covered by some of these companies to attend previous scientific meetings including ERS and AAAAI; has provided expert testimony for Barr Pharmaceuticals; and has participated in clinical research studies sponsored by AstraZeneca, GlaxoSmithKline, Merck Sharpe and Dohme, and Novartis. ERB has served as a consultant to AstraZeneca, Boehringer Ingelheim, Genentech, GlaxoSmithKline, Johnson and Johnson, and Merck; and has performed clinical trials for AstraZeneca, Boehringer Ingelheim, Cephalon, Forest, Genentech, GlaxoSmithKline, KalaBios, MedImmune, Novartis and Sanofi-Aventis, which have been administered by his employer Wake Forest University School of Medicine. WWB has served as a consultant for Amgen, AstraZeneca, Boehringer Ingelheim, Genentech, GlaxoSmithKline, MedImmune, Novartis and TEVA; served on advisory boards for Altair, Amgen, Centocor, GlaxoSmithKline, Johnson & Johnson, Merck Sharpe and Dohme and Pfizer; received lecture fees from Merck Sharpe and Dohme; and received research funding from AstraZeneca, Ception, GlaxoSmithKline, MedImmune and Novartis. PMO'B has served as a consultant to AstraZeneca, Almirall, Boehringer Ingelheim, GlaxoSmithKline and Merck; has served on advisory boards for AIM, Altair, Boehringer Ingelheim, GlaxoSmithKline, MedImmune and Merck; has received lecture fees from Chiesi; and has received research funding from Amgen, AstraZeneca, Asmacure, Genentech and Ono. AW has served as a consultant to Almirall, Chiesi, Cytos, and GlaxoSmithKline; and has received lecture fees and research grants from GlaxoSmithKline. EDB has served as a consultant to AlkAbello, Almirall, Boehringer Ingelheim, Cephalon, Hoffman la Roche, ICON, IMS Consulting Group,

and Navigant Consulting; been on advisory boards for Almirall, AstraZeneca, Boehringer Ingelheim, Elevation Pharma, Forest, GlaxoSmithKline, Merck, Napp, Novartis, Nycomed and Takeda; and received lecture fees from AlkAbello, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, Pfizer, Takeda and TEVA; and his institution has received remuneration for participation in clinical trials sponsored by Actelion, Aeras, Almirall, AstraZeneca, Boehringer Ingelheim, Forest, GlaxoSmithKline, Hoffman La Roche, Merck, Novartis, Takeda and TEVA. EMK has served on advisory boards, speaker panels, or received travel reimbursement with AstraZeneca, Forest, Ironwood, Merck, Mylan, Novartis, Pearl, Pfizer, Sanofi-Aventis, Sunovion and Targacept. He has conducted multicentre clinical research trials for approximately 70 pharmaceutical companies including GlaxoSmithKline. SS, RF, and LJ are employees of and hold stock in GlaxoSmithKline.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.rmed.2013.11.009>

References

- [1] Global Initiative for Asthma. Global strategy for asthma management and prevention [accessed 26.07.13], <http://www.ginasthma.org/Guidelines/guidelines-resources.html>; 2012.
- [2] Hermosa JL, Sánchez CB, Rubio MC, Mínguez MM, Walther JL. Factors associated with the control of severe asthma. *J Asthma* 2010;47:124–30.
- [3] Sims EJ, Price D, Haughney J, Ryan D, Thomas M. Current control and future risk in asthma management. *Allergy Asthma Immunol Res* 2011;3:217–25.
- [4] Biggadike K, Bledsoe RK, Hassell AM, Kirk BE, McLay IM, Shewchuk LM, et al. X-ray crystal structure of the novel enhanced-affinity glucocorticoid agonist fluticasone furoate in the glucocorticoid receptor-ligand binding domain. *J Med Chem* 2008;51:3349–52.
- [5] Salter M, Biggadike K, Matthews JL, West MR, Haase MV, Farrow SN, et al. Pharmacological properties of the enhanced-affinity glucocorticoid fluticasone furoate in vitro and in an in vivo model of respiratory inflammatory disease. *Am J Physiol Lung Cell Mol Physiol* 2007;293:660–7.
- [6] Ito K, Rossios C, Adcock IM, Barnes PJ, Johnson M. Fluticasone furoate, a novel enhanced-affinity inhaled corticosteroid (ICS), with sustained glucocorticoid receptor nuclear translocation. *Am J Respir Crit Care Med* 2010;181(Suppl.):A5409.
- [7] Woodcock A, Bleecker ER, Busse WW, Lötvalld J, Snowise NG, Frith L, et al. Fluticasone furoate: once-daily evening treatment versus twice-daily treatment in moderate asthma. *Respir Res* 2011;12:160.
- [8] Bateman ED, Bleecker ER, Lötvalld J, Woodcock A, Forth R, Medley H, et al. Dose effect of once-daily fluticasone furoate in persistent asthma: a randomized trial. *Respir Med* 2012;106:642–50.
- [9] Bleecker ER, Bateman ED, Busse WW, Woodcock A, Frith L, House KW, et al. Once-daily fluticasone furoate is efficacious in patients with symptomatic asthma on low-dose inhaled corticosteroids. *Ann Allergy Asthma Immunol* 2012;109:353–8.
- [10] Busse WW, Bleecker ER, Bateman ED, Lötvalld J, Forth R, Davis AM, et al. Fluticasone furoate demonstrates efficacy in patients with asthma symptomatic on medium doses of inhaled corticosteroid therapy: an 8-week, randomised, placebo-controlled trial. *Thorax* 2012;67:35–41.
- [11] Oliver A, Quinn D, Goldfrad C, van Hecke B, Ayer J, Boyce M. Combined fluticasone furoate/vilanterol reduces decline in lung function following inhaled allergen 23 h after dosing in adult asthma: a randomised, controlled trial. *Clin Transl Allergy* 2012;2:11.
- [12] Avamys (fluticasone furoate) indicated for the treatment of symptoms of allergic rhinitis: summary of product characteristics. European Medicines Agency authorisation codes EU/1/07/434/001; EU/1/07/434/002; EU/1/07/434/003. http://www.emea.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000770/WC500028814.pdf [accessed 26.07.13].
- [13] Veramyst (fluticasone furoate) nasal spray. US prescribing information. Research Triangle Park, NC, USA: GlaxoSmithKline; 2011 [accessed 26.07.13], http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022051s007lbl.pdf.
- [14] Lötvalld J, Bleecker ER, Busse WW, P. O'Byrne, Woodcock A, Bateman E, et al. Efficacy and safety of once-daily fluticasone furoate (FF) in patients with persistent asthma: a 24-week randomised trial. In: Presented at the Annual Congress of the European Respiratory Society, 1–5 September 2012, Vienna, Austria Poster P2123.
- [15] National Institutes of Health. Guidelines for the diagnosis and management of asthma – expert panel report 3. Bethesda, MD: US Department of Health and Human Services; 2007. NIH Publication No. 07–4051.
- [16] Hankinson JL, Kawut SM, Shahar E, Smith LJ, Stukovsky KH, Barr RG. Performance of American Thoracic Society-recommended spirometry reference values in a multiethnic sample of adults. *Chest* 2010;137:138–45.
- [17] Woodcock A, Bateman ED, Busse WW, Lötvalld J, Snowise NG, Forth R, et al. Efficacy in asthma of once-daily treatment with fluticasone furoate: a randomized, placebo-controlled trial. *Respir Res* 2011;12:132.
- [18] Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA, et al. Can guideline-defined asthma control be

- achieved? the gaining optimal asthma control study. *Am J Respir Crit Care Med* 2004;170:836–44.
- [19] Schatz M, Kosinski M, Yarlas AS, Hanlon J, Watson ME, Jhingran P. The minimally important difference of the asthma control test. *J Allergy Clin Immunol* 2009;124:719–23.
- [20] Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific quality of life instrument. *J Clin Epidemiol* 1994;47:81–7.
- [21] Adams NP, Bestall JC, Lasserson TJ, Jones P, Cates CJ. Fluticasone versus placebo for chronic asthma in adults and children. *Cochrane Database Syst Rev* 2008;4. CD003135.
- [22] Lötvalld J, Ekerljung L, Rönmark EP, Wennergren G, Lindén A, Rönmark E, et al. West Sweden asthma study: prevalence trends over the last 18 years argues no recent increase in asthma. *Respir Res* 2009;10:94.
- [23] Bae JP, Dobesh PP, Klepser DG, Anderson JD, Zagar AJ, McCollam PL, et al. Adherence and dosing frequency of common medications for cardiovascular patients. *Am J Manag Care* 2012;18:139–46.
- [24] Flack JM, Nasser SA. Benefits of once-daily therapies in the treatment of hypertension. *Vasc Health Risk Manag* 2011;7:777–87.
- [25] Navaratnam P, Friedman HS, Urdaneta E. Treatment with inhaled mometasone furoate reduces short-acting $\beta(2)$ agonist claims and increases adherence compared to fluticasone propionate in asthma patients. *Value Health* 2011;14:339–46.
- [26] Friedman HS, Navaratnam P, McLaughlin J. Adherence and asthma control with mometasone furoate versus fluticasone propionate in adolescents and young adults with mild asthma. *J Asthma* 2010;47:994–1000.
- [27] Jentzsch NS, Camargos P, Sarinho ES, Bousquet J. Adherence rate to beclomethasone dipropionate and the level of asthma control. *Respir Med* 2012;106:338–43.
- [28] Bleecker ER, Lötvalld J, O'Byrne PM, Woodcock A, Busse WW, Forth R, Medley H, Nunn C, Jacques L, Bateman ED. Efficacy of fluticasone furoate (FF) as a monotherapy and in combination with vilanterol (VI) over 12 weeks in patients with persistent asthma. *Eur Respir J* 2012;40(Suppl. 56):370s.
- [29] Woodcock A, Bleecker ER, Lötvalld J, O'Byrne PM, Bateman ED, Medley H, Ellsworth A, Jacques L, Busse WW. Efficacy and safety of fluticasone furoate/vilanterol compared with fluticasone propionate/salmeterol combination in adult and adolescent patients with persistent asthma: a randomized trial. *Chest* 2013;144:1222–9.
- [30] O'Byrne PM, Bleecker ER, Bateman ED, Busse WW, Woodcock A, Forth R, Toler WT, Jacques L, Lötvalld J. Once-daily fluticasone furoate alone or combined with vilanterol in persistent asthma. *Eur Respir J* 2013. Oct 17 [Epub ahead of print].
- [31] Busse WW, O'Byrne PM, Bleecker ER, Lötvalld J, Woodcock A, Andersen L, Hicks W, Crawford J, Jacques L, Apoux L, Bateman ED. Safety and tolerability of the novel inhaled corticosteroid fluticasone furoate in combination with the β_2 agonist vilanterol administered once daily for 52 weeks in patients ≥ 12 years old with asthma: a randomised trial. *Thorax* 2013;68:513–20.
- [32] Allen A, Schenkenberger I, Trivedi R, Cole J, Hicks W, Gul N, Jacques L. Inhaled fluticasone furoate/vilanterol does not affect hypothalamic-pituitary-adrenal axis function in adolescent and adult asthma: randomised, double-blind, placebo-controlled study. *Clin Respir J* 2013;7:397–406.
- [33] Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy: a systemic review and meta-analysis. *Arch Intern Med* 1999;159:941–55.
- [34] Barnes PJ. Inhaled corticosteroids. *Pharmaceuticals* 2010;3:514–40.
- [35] Ahmet A, Kim H, Spier S. Adrenal suppression: a practical guide to the screening and management of this under-recognized complication of inhaled corticosteroid therapy. *Allergy Asthma Clin Immunol* 2011;7:13.
- [36] Peters JM, Avol E, Navidi W, London SJ, Gauderman WJ, Lurmann F, et al. A study of twelve Southern California communities with differing levels and types of air pollution: I. Prevalence of respiratory morbidity. *Am J Respir Crit Care Med* 1999;159:760–7.
- [37] Chalmers GW, Macleod KJ, Little SA, Thomson LJ, McSharry CP, Thomson NC. Influence of cigarette smoking on inhaled corticosteroid treatment in mild asthma. *Thorax* 2002;57:226–30.
- [38] Tomlinson JE, McMahon AD, Chaudhuri R, Thompson JM, Wood SF, Thomson NC. Efficacy of low and high dose inhaled corticosteroid in smokers versus non-smokers with mild asthma. *Thorax* 2005;60:282–7.