ORIGINAL ARTICLE

Once-daily fluticasone furoate 50 mcg in mild-to-moderate asthma: a 24-week placebo-controlled randomized trial

W. W. Busse[1], E. D. Bateman[2], P. M. O'Byrne[3], J. Lötvall[4], A. Woodcock[5], H. Medley[6], R. Forth[7] & L. Jacques[6]

[1]Department of Medicine, University of Wisconsin, Madison, WI, USA; [2]Department of Medicine, University of Cape Town, Cape Town, South Africa; [3]Michael G DeGroote School of Medicine, Hamilton, ON, Canada; [4]Krefting Research Centre, University of Gothenburg, Gothenburg, Sweden; [5]Institute of Inflammation and Repair, University of Manchester, Manchester; [6]Respiratory Medicines Development Centre, GlaxoSmithKline, London, UK; [7]Quantitative Sciences Division, GlaxoSmithKline, Research Triangle Park, NC, USA

Abstract

Background: Inhaled glucocorticosteroids (ICS) are the mainstay of treatment in asthma. Fluticasone furoate (FF) is a novel, once-daily ICS asthma therapy. This study investigated the efficacy and safety of FF 50 mcg in patients with mild-to-moderate persistent asthma.

Methods: A 24-week, multicenter, randomized, placebo-controlled and active-controlled, double-blind, double-dummy, parallel-group phase III study. Three hundred and fifty-one patients (aged ≥12 years; uncontrolled by non-ICS therapy) were randomized to treatment (1 : 1 : 1) with once-daily FF 50 mcg dosed in the evening, twice-daily fluticasone propionate (FP) 100 mcg or placebo. The primary endpoint was change from baseline in evening trough forced expiratory volume in 1 s (FEV_1) at Week 24. Secondary endpoints were change from baseline in the percentage of rescue-free 24-h periods (powered endpoint), change from baseline in evening and morning peak expiratory flow, change from baseline in the percentage of symptom-free 24-h periods and number of withdrawals due to lack of efficacy.

Results: Evening trough FEV_1 at Week 24 was not statistically significantly increased with FF 50 mcg once-daily (37 ml [95% CI: −55, 128]; $P = 0.430$), but was with FP 100 mcg twice daily (102 ml [10, 194]; $P = 0.030$), *vs* placebo. No consistent trends were observed across other endpoints, including the powered secondary endpoint. No safety concerns were raised for either active treatment.

Conclusions: FP 100 mcg twice daily improved evening trough FEV_1 in patients with mild-to-moderate persistent asthma, but FF 50 mcg once daily did not demonstrate a significant effect. Secondary endpoints showed variable results. No safety concerns were identified for FF or FP.

Inhaled glucocorticosteroids (ICS) improve lung function and asthma control and are the mainstay of treatment for all severities of asthma (1, 2). Levels of poorly controlled asthma remain high despite the availability of effective anti-inflammatory treatments (3). Multiple factors are perceived to contribute to poor control, including suboptimal adherence to maintenance therapy (4). One approach to improving adherence is to reduce the frequency of dosing from twice daily to once daily (5–7).

Fluticasone furoate (FF) is a new once-daily ICS for the treatment of asthma. FF is structurally distinct from fluticasone propionate (FP) (8) and has a longer duration of action

in vitro (9). Once-daily FF at doses of 50–200 mcg has demonstrated efficacy with a good safety and tolerability profile in patients with asthma (10–12).

A *post hoc* analysis of previous dose-ranging studies suggested that FF dosed at 50 mcg is more effective for patients with less severe asthma (>65% predicted forced expiratory volume in 1s [FEV_1]) than those with more severe disease (≤65% predicted FEV_1) (13). Therefore, the objective of this placebo-controlled study was to evaluate the efficacy and safety of once-daily FF 50 mcg in patients with persistent asthma uncontrolled (>60% predicted FEV_1) by non-ICS therapy. Twice-daily FP 100 mcg was an active control,

which is indicated as a low-dose treatment for asthma and was considered to be an appropriate step-up therapy for patients uncontrolled with SABA alone. The results of this *post hoc* analysis have been published in abstract form (14).

Methods

Patients

Patients aged ≥ 12 years, diagnosed with asthma as defined by the NIH (15) for ≥ 12 weeks, using noncorticosteroid controllers and/or short-acting beta$_2$-agonists (SABAs), demonstrating best $FEV_1 \geq 60\%$ predicted and reversibility of $\geq 12\%$ and ≥ 200 ml following 2–4 inhalations of salbutamol at screening were eligible. ICS or long-acting beta$_2$-agonist (LABA) use within 4 weeks of screening was not permitted. Further exclusion criteria are presented in Appendix S1.

Patients stopped using noncorticosteroid controllers, and existing SABA medication was replaced with salbutamol at screening; salbutamol was not permitted within 6 h of clinic visits. After a 2-week run-in, patients with evening FEV_1 $\geq 60\%$ predicted and documented salbutamol use and/or asthma symptoms on ≥ 4 of the previous 7 days who had completed all morning and evening diary measures on ≥ 4 of the previous 7 days were randomized. Exclusion criteria at randomization are summarized in Appendix S1.

All patients gave written informed consent prior to study entry. The study was approved by local ethics review committees and was conducted in accordance with the Declaration of Helsinki (16), Good Clinical Practice guidelines (17) and all applicable regulatory requirements.

Study design and treatments

This phase III, multicenter, randomized, placebo-controlled and active-controlled, double-blind, double-dummy, and parallel-group study (GSK study number FFA115285; www. clinicaltrials.gov registration number NCT01436110) was conducted at 34 centers in six countries (United States, Poland, Russia, Peru, Mexico, and the Netherlands) between September 21, 2011 and September 26, 2012. Patients were randomized (1 : 1 : 1) to receive (i) FF 50 mcg once daily in the evening via the ELLIPTA® dry powder inhaler (DPI) (emitted dose 46 mcg) and placebo DISKUS®[1] morning and evening; (ii) FP 100 mcg twice daily via DISKUS inhaler and placebo ELLIPTA in the evening; or (iii) placebo ELLIPTA in the evening and placebo DISKUS twice daily. Patients were assigned to study treatment following a telephone call to the Registration and Medication Ordering System (RAMOS [GlaxoSmithKline, UK]) and randomized in accordance with a central randomization schedule generated by the sponsor using a validated computerized system (RandAll [GlaxoSmithKline, UK]). Study visits occurred at weeks 2, 4, 8, 12, 18, and 24, with a follow-up visit at Week 25; telephone contact at weeks 16 and 22 helped to monitor compliance. Patients recorded

[1]ELLIPTA® and DISKUS® are trademarks of the GSK group of companies.

peak expiratory flow (PEF) measurements and symptoms twice daily on an electronic diary card. Restricted concomitant medications are shown in Appendix S2.

Outcome measurements

The primary endpoint was change from baseline in evening predose, prebronchodilator (trough) FEV_1 at Week 24. The powered secondary endpoint was change from baseline in the percentage of rescue-free 24-h periods during the 24-week treatment period. Other secondary endpoints were as follows: change from baseline in evening and morning PEF averaged over 24 weeks, change from baseline in the percentage of symptom-free 24-h periods over 24 weeks, and number of withdrawals due to lack of efficacy during the treatment period. Other endpoints included change from baseline in Asthma Control Test™ (ACT) score, percentage of patients with ACT score ≥ 20, change from baseline in Total Asthma Quality of Life Questionnaire (AQLQ[+12]) score (all at Week 24) and unscheduled asthma-related healthcare resource utilization.

Safety endpoints were incidence of adverse events (AEs) and of protocol-defined severe asthma exacerbations during the treatment period. AEs were coded using the Medical Dictionary for Regulatory Activities. Suspected pneumonia was confirmed by X-ray.

Statistical analysis

Recruitment of 330 patients was expected to give 104 evaluable patients per treatment group. This would provide 94% power to detect a 200 ml treatment difference in trough FEV_1, and 95% power to detect a treatment difference of 15% change from baseline in percentage of rescue-free 24-h periods for FF *vs* placebo. The overall power to detect treatment differences for FF *vs* placebo across the primary and powered secondary endpoints was 90%.

The primary and secondary endpoints of rescue-free and symptom-free 24-h periods and evening and morning PEF were analyzed using an analysis of covariance (ANCOVA) model adjusted for baseline, region, gender, age, and treatment group. An additional sensitivity analysis was performed for the primary endpoint using a repeated measures model adjusted for baseline FEV_1, region, gender, age, visit, and treatment group. This model also contained interaction terms for visit-by-treatment and visit-by-baseline interaction term. Withdrawals due to lack of efficacy were analyzed using Fisher's Exact test. Details of analyses used for the other endpoints are summarized in Appendix S3. The intent-to-treat (ITT) population was the primary population for all efficacy and safety analyses, and comprised all patients that were randomized and received at least one dose of study medication.

Data were analyzed using a closed, step-down statistical hierarchy, whereby failure to achieve significance ($P < 0.05$) for the primary treatment comparison of FF *vs* placebo, at any point in the hierarchy, meant that statistical significance could not be inferred for the remaining endpoints, and these would be interpreted as descriptive only. The hierarchy order was as follows: (i) trough FEV_1, (ii) rescue-free 24-h periods,
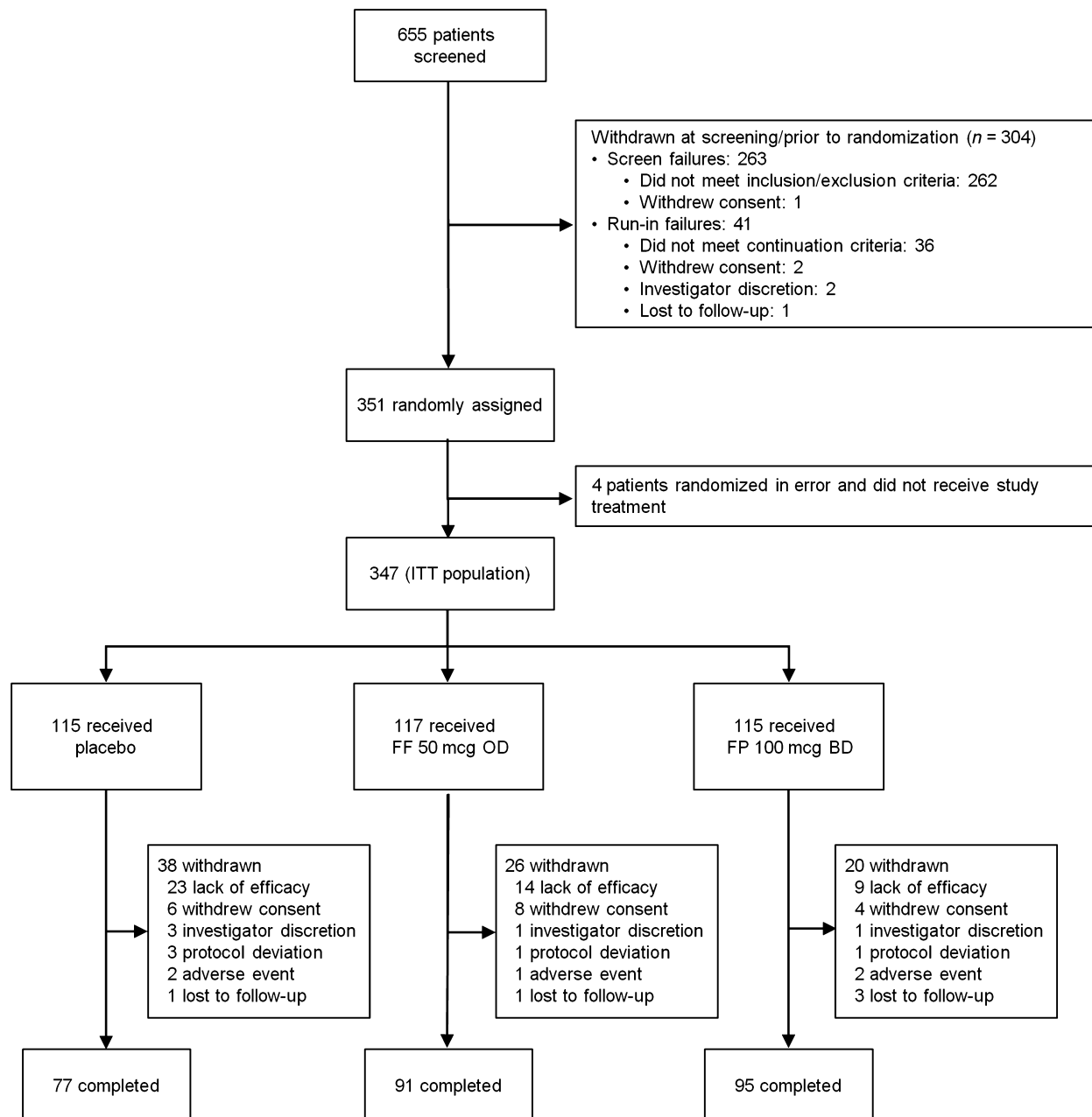
```
                        ┌─────────────────┐
                        │  655 patients   │
                        │    screened     │
                        └────────┬────────┘
                                 │
                                 │        ┌────────────────────────────────────────────────────┐
                                 │        │ Withdrawn at screening/prior to randomization (n = 304) │
                                 │        │ • Screen failures: 263                              │
                                 ├───────▶│    • Did not meet inclusion/exclusion criteria: 262 │
                                 │        │    • Withdrew consent: 1                            │
                                 │        │ • Run-in failures: 41                               │
                                 │        │    • Did not meet continuation criteria: 36         │
                                 │        │    • Withdrew consent: 2                            │
                                 │        │    • Investigator discretion: 2                     │
                                 │        │    • Lost to follow-up: 1                           │
                                 │        └────────────────────────────────────────────────────┘
                                 │
                        ┌────────▼────────┐
                        │ 351 randomly    │
                        │   assigned      │
                        └────────┬────────┘
                                 │        ┌────────────────────────────────────────────────────┐
                                 ├───────▶│ 4 patients randomized in error and did not receive study │
                                 │        │ treatment                                          │
                                 │        └────────────────────────────────────────────────────┘
                        ┌────────▼────────┐
                        │ 347 (ITT        │
                        │  population)    │
                        └────────┬────────┘
```

Figure 1 Patient disposition. FF, fluticasone furoate; FP, fluticasone propionate; ITT, intent-to-treat.

115 received placebo	117 received FF 50 mcg OD	115 received FP 100 mcg BD
38 withdrawn 23 lack of efficacy 6 withdrew consent 3 investigator discretion 3 protocol deviation 2 adverse event 1 lost to follow-up	**26 withdrawn** 14 lack of efficacy 8 withdrew consent 1 investigator discretion 1 protocol deviation 1 adverse event 1 lost to follow-up	**20 withdrawn** 9 lack of efficacy 4 withdrew consent 1 investigator discretion 1 protocol deviation 2 adverse event 3 lost to follow-up
77 completed	91 completed	95 completed

(iii) evening PEF, (iv) morning PEF, (v) symptom-free 24-h periods, (vi) withdrawals due to lack of efficacy.

Results

Study population

Six hundred and fifty-five patients were screened, 351 were randomized, 347 were included in the ITT population, and 263 (76%) completed the study (Fig. 1). Patient demographics and screening/baseline characteristics were similar across treatment groups (Table 1). Adolescents (aged 12–17 years) comprised 15% of the ITT population. Mean % predicted FEV_1 at baseline was high across all treatment groups (80.65–81.63%). Use of concomitant medications is summarized in Appendix S4. Treatment compliance was high across all treatment groups with ELLIPTA (97.5–98.6%) and DISKUS (93.7–95.0%).

Table 1 Patient demographics and lung function at screening/baseline (intent-to-treat population)

	Placebo (n = 115)	FF 50 mcg OD PM (n = 117)	FP 100 mcg BD (n = 115)	Total (N = 347)
Age, mean (SD), years	37.6 (18.03)	35.4 (14.64)	36.2 (16.95)	36.4 (16.57)
Age range, years	12–77	12–77	12–81	12–81
Gender: female, n (%)	81 (70)	72 (62)	76 (66)	229 (66)
Race, n (%)				
White	52 (45)	55 (47)	54 (47)	161 (46)
American Indian or Alaska Native	31 (27)	30 (26)	34 (30)	95 (27)
American Indian or Alaska Native and White	21 (18)	16 (14)	18 (16)	55 (16)
African American/African Heritage	9 (8)	14 (12)	9 (8)	32 (9)
Other*	2 (2)	2 (2)	0	4 (1)
Percent reversibility FEV_1†, %	22.98 (11.090)	21.49 (8.247)	23.46 (10.459)	22.64 (10.003)
Baseline characteristics, mean (SD)				
Prebronchodilator FEV_1 (l)	2.475 (0.7395)	2.653 (0.6834)	2.582 (0.8065)	2.571 (0.7460)
Percent predicted FEV_1, %	80.65 (13.396)	81.63 (12.566)	80.77 (14.485)	81.02 (13.468)
Rescue-free 24-h periods, %	11.1 (24.01)	11.8 (26.25)	6.7 (17.20)	NA
Symptom-free 24-h periods, %	4.3 (13.48)	7.1 (20.61)	5.4 (18.27)	NA

BD, twice daily; FEV_1, forced expiratory volume in 1 s; FF, fluticasone furoate; FP, fluticasone propionate; NA, not applicable; OD, once daily; PM, evening; SD, standard deviation.

*Other = Asian, African American/African Heritage and American Indian or Alaska Native, and Asian and White.

†Recorded at screening. n = 144, 116, 114, and 344, respectively, for the Placebo, FF 50 mcg OD, FP 100 mcg BD, and Total groups.

Efficacy

Primary endpoint

Improvement in change from baseline in predose evening trough FEV_1 at Week 24 was not significant *vs* placebo for FF (37 ml, P = 0.430), but was for FP (102 ml, P = 0.030) (Table 2). The repeated measures analysis showed sustained improvement in trough FEV_1 over the treatment period in all treatment groups, which was not statistically significant for either treatment *vs* placebo at Week 24 (Fig. 2). Because of the statistical hierarchy, the lack of statistical significance on the primary endpoint meant that all subsequent endpoints were interpreted as descriptive only for the FF *vs* placebo treatment comparison.

Powered secondary endpoint

The percentage of rescue-free 24-h periods increased from baseline over Weeks 0–24 in all treatment groups (Table 2); mean improvements, *vs* placebo, were not statistically significant for FF (7.8%; 95% confidence interval [CI]: −1.0, 16.7), but were for FP (10.6%; 95% CI: 1.7, 19.6). The number of additional rescue-free days per week, *vs* placebo, was similar for FF (0.5) and FP (0.7).

Secondary and other endpoints

Over the 24-week treatment period, mean change (95% CI) from baseline *vs* placebo in evening PEF was 17.2 l/min (5.9, 28.6) for FF and 4.3 l/min (−7.0, 15.7) for FP (Fig. 3); change in morning PEF was 19.2 l/min (8.5, 29.9) for FF and 10.6 l/min (−0.2, 21.3) for FP. Changes from baseline in percentage of symptom-free 24-h periods, *vs* placebo, were 8.3 (0.3, 16.3) for FF and 7.5 (−0.5, 15.5) for FP (Fig. 3). The equivalent number of additional symptom-free days per week, *vs* placebo, was similar for FF (0.6) and FP (0.5). There were more withdrawals due to lack of efficacy with placebo (20%) than with FF (12%) or FP (8%) (Appendix S5).

Mean change (95% CI) from baseline in ACT score, *vs* placebo, was 0.9 (−0.1, 2.0) with FF and 1.0 (−0.1, 2.0) with FP (Fig. 3). Most (87–90%) patients reported an ACT score <20 at baseline; a greater proportion of patients receiving FF (65%) and FP (63%) than placebo (56%) reported an ACT score ≥20 at Week 24. No improvement over placebo was seen in AQLQ (+12) score with either active treatment (Fig. 3). Seven patients reported unscheduled healthcare resource utilization (4 placebo, 2 FF, 1 FP), five due to a severe asthma exacerbation (4 placebo, 1 FF).

Safety assessments

The incidence of on-treatment AEs was 48–56% across treatment groups, with headache, nasopharyngitis, pharyngitis, and upper respiratory tract infections occurring most frequently overall (Table 3). Five patients withdrew due to AEs: n = 2 with placebo (respiratory tract infection; pneumonia); n = 1 with FF (apathy, fatigue, irritability, and weight increase); n = 2 with FP (n = 1: dermatitis; n = 1: dyspnea and sensory disturbance, both of which were ongoing at last contact). The incidence of treatment-related AEs was 3% in all treatment groups (n = 3 placebo, 4 FF, 4 FP). AEs of special interest were reported by 27 patients (12 placebo, 4 FF, 11 FP). Oral candidiasis (n = 2 with FF) and oral candidiasis and dysphonia (n = 1 with FP) were the only AEs that were both associated with ICS and considered treatment related.

Four patients experienced on-treatment serious AEs, three with placebo (pneumonia, cholelithiasis, and premenstrual

Table 2 Statistical analysis of primary (change from baseline in trough FEV$_1$) and powered secondary endpoints at Week 24 (intent-to-treat population)

	Placebo (n = 115)	FF 50 mcg OD PM (n = 117)	FP 100 mcg BD (n = 115)
Trough FEV$_1$ (Week 24), ml*			
n	111	116	112
LS mean	2653	2690	2755
LS mean change from baseline (SE)	89 (33.1)	126 (32.3)	191 (32.8)
Treatment difference vs placebo (95% CI)		37 (−55, 128)	102 (10, 194)
		P = 0.430	P = 0.030
Percentage of rescue-free 24-h periods (Weeks 1–24)			
n	114	116	113
LS mean change from baseline, % (SE)	21.1 (3.20)	28.9 (3.17)	31.7 (3.21)
Treatment difference vs placebo (95% CI)†		7.8 (−1.0, 16.7)	10.6 (1.7, 19.6)

BD, twice daily; CI, confidence interval; FEV$_1$, forced expiratory volume in 1 s; FF, fluticasone furoate; FP, fluticasone propionate; LS, least squares; NA, not applicable; OD, once daily; PM, evening; SE, standard error.

Analysis performed using ANCOVA with covariates of baseline, region, gender, age, and treatment.

*Last observation carried forward (LOCF) was used to impute missing data.

†No inferences (P-values) provided as primary treatment comparison was not statistically significant.

syndrome) and one with FP (dermatitis); none were considered treatment related, and only the incidence of pneumonia with placebo and the incidence of dermatitis with FP led to withdrawal. There were no post-treatment serious AEs and no deaths. Severe asthma exacerbations were experienced by more patients with placebo (n = 7) than with FF (n = 3) or FP (n = 1); all exacerbations were treated with systemic/oral corticosteroids. Pneumonia was confirmed by chest X-ray in two patients (1 placebo, 1 FP); neither was considered to be treatment related.

Discussion

Significant treatment benefits were not observed for the primary endpoint of change from baseline in evening trough FEV$_1$ or for the secondary endpoint of change from baseline in percentage of rescue-free 24-h periods for the comparison of once-daily FF 50 mcg vs placebo in patients with mild-to-moderate asthma; however, there were numerical improvements with FF 50 mcg. Significant treatment benefits were observed for the comparison of twice-daily FP 100 mcg vs placebo. This study was not powered to formally compare FF with FP; furthermore, no consistent trend was observed in any treatment group across the remaining endpoints. No safety concerns were identified for once-daily FF 50 mcg or twice-daily FP 100 mcg.

GINA guidelines recommend using the lowest dose of ICS possible to maintain control of asthma (2). Thus, the purpose of our study was to investigate FF 50 mcg as a potentially appropriate dose in patients with mild-to-moderate asthma (FEV$_1$ ≥60% predicted, not using ICS). The finding that FF 50 mcg was not significantly better than placebo in improving
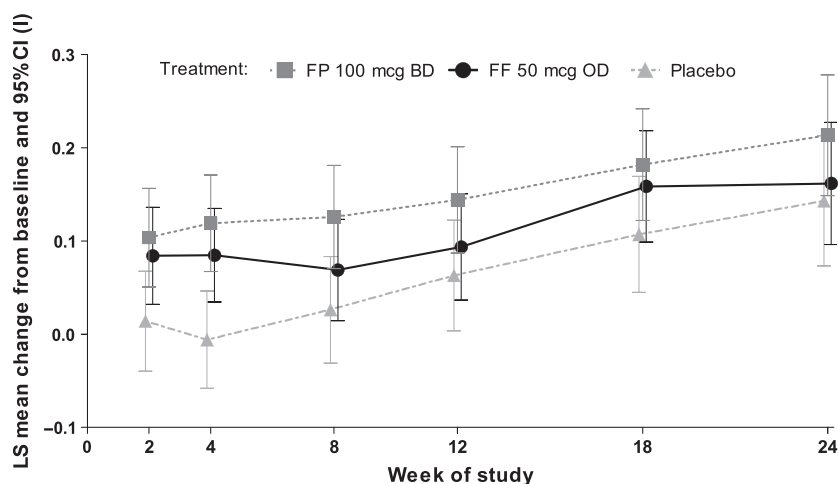
Figure 2 Repeated measures analysis of mean change from baseline (95% CI) in trough FEV$_1$ (l) (intent-to-treat population). BD, twice daily; CI, confidence interval; FEV$_1$, forced expiratory volume in 1 s; FF, fluticasone furoate; FP, fluticasone propionate; LS, least squares; OD, once daily.
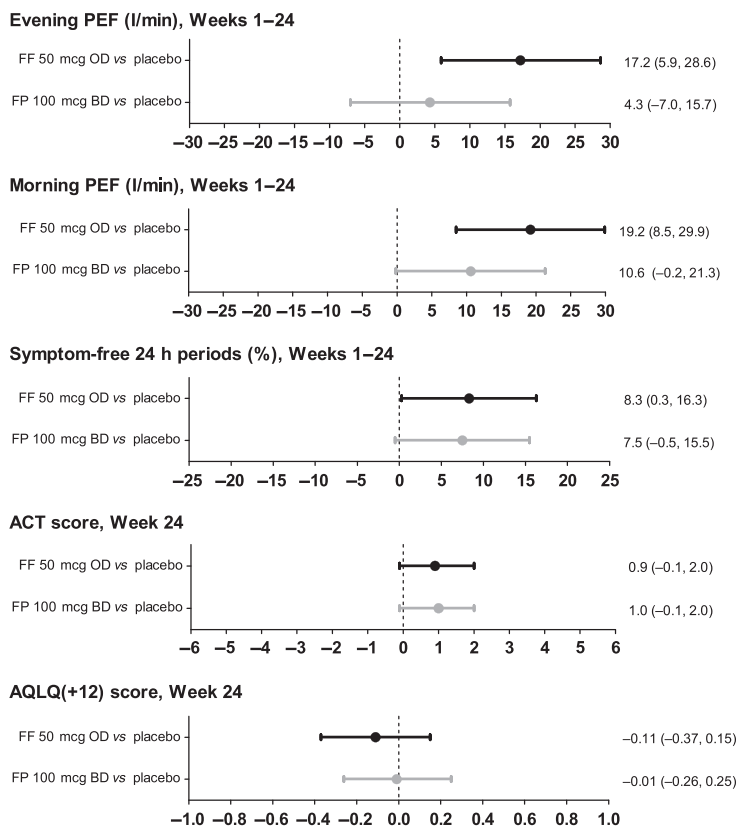
Figure 3 Summary of change from baseline for selected secondary and other efficacy endpoints (intent-to-treat population). Due to the failure to achieve statistical significance of the primary endpoint in the statistical hierarchy, data for these endpoints can be interpreted as descriptive only. Data are mean and 95% confidence interval. AM, morning; BD, twice daily; FF, fluticasone furoate; FP, fluticasone propionate; OD, once daily; PM, evening.

evening trough FEV_1 is not consistent with previous observations. Other studies in similar patient populations have reported statistically significant effects of once-daily FF 50 mcg, vs placebo, on evening trough FEV_1 when dosed for 8 weeks (129 ml, $P = 0.033$) (10) or 12 weeks (120 ml, $P = 0.012$) (18). There are a number of possible explanations for the discrepant findings. In our study, patients had a baseline mean % predicted FEV_1 of 81.02%; therefore, a ceiling effect may have limited the potential for a response to treatment relative to more patients with severe asthma (% predicted FEV_1 <70%) (19), as were included in the 8-week study (10). Assessment of morning trough FEV_1 may have maximized the opportunity to detect a difference, as lung function is naturally at a minimum at this time (20); however, a similar patient population was treated with FF 50 mcg in the 12-week study (18), contradicting this possible explanation. Additionally, in this study, the mean prebronchodilator FEV_1 improved by 143 ml during run-in, indicating that 2 weeks may not have been long enough to minimize the placebo response during the study. These explanations are unlikely to explain fully the lack of significance for the primary endpoint with FF, as statistical significance relative to placebo was achieved ($P < 0.05$) with FP, showing that the study had assay

sensitivity to detect a treatment difference. The FP findings conflict with those from the 8-week study (10) in which FP 100 mcg twice daily did not significantly improve trough FEV_1 compared with placebo, suggesting that low-dose ICS will demonstrate efficacy in some studies, but not in others, and that some patients with mild-to-moderate asthma who are uncontrolled with SABA alone will require further step-up therapy. In other studies, higher doses of FF once-daily have proven to be as efficacious as FP twice-daily. FF 100 mcg once-daily demonstrated similar efficacy to FP 250 mcg twice daily across a range of endpoints (21), and FF 200 mcg once-daily has demonstrated similar efficacy to FP 500 mcg twice-daily in improving trough FEV_1 over 24 weeks, in patients with moderate-to-severe persistent asthma (22).

No statistical inference could be drawn for FF, vs placebo, for any of the remaining endpoints because of the statistical hierarchy. Increases from baseline in rescue-free and symptom-free 24-h periods were observed in all treatment groups with numerical improvements relative to placebo observed for FF and FP; improvements in rescue-free 24-h periods were statistically significant with FP, but not with FF. The improvements with FF 50 mcg were smaller than those observed in previous studies over 8 weeks (10) and 12 weeks (18).

Table 3 Summary of most frequent on-treatment AEs and serious AEs (safety population)

	Placebo (n = 115)	FF 50 mcg OD PM (n = 117)	FP 100 mcg BD (n = 115)
AEs			
On-treatment	64 (56)	56 (48)	59 (51)
On-treatment, treatment related*	3 (3)	4 (3)	4 (3)
On-treatment, leading to withdrawal	2 (2)	1 (<1)	2 (2)
Post-treatment	0	0	1 (<1)
Serious AEs			
On-treatment	3 (3)	0	1 (<1)
On-treatment AEs occurring in ≥5% patients in any treatment group			
Headache	13 (11)	17 (15)	12 (10)
Nasopharyngitis	6 (5)	8 (7)	12 (10)
Pharyngitis	10 (9)	7 (6)	5 (4)
Upper respiratory tract infection	3 (3)	6 (5)	6 (5)
Influenza	4 (3)	4 (3)	6 (5)
Oropharyngeal pain	6 (5)	0	2 (2)

AE, adverse event; BD, twice daily; FF, fluticasone furoate; FP, fluticasone propionate; OD, once daily; PM, evening.
All data are n (%).
*Adverse events deemed treatment related by the investigator prior to unblinding.

Poor correlation between treatment effects on FEV_1 and PEF was seen in our study and although unusual, such poor correlation has been observed by others (23, 24). Despite changes in FEV_1 with FF not being significantly better than placebo, numerical improvements in evening and morning PEF, vs placebo, were large. The opposite was observed with FP and improvements in PEF were modest and not statistically significant. Although significance cannot be inferred for the PEF endpoints, the observed numerical improvements with FF may be relevant because of patients' limited volume for improvement in FEV_1. No clinically meaningful improvements in ACT (+≥3) (25) or Total AQLQ (+12) (+≥0.5) (26) score were observed with either active treatment compared with placebo, findings that accord with those from the 12-week study (18).

No safety concerns were raised for FF or FP. The incidence of AEs was similar in all three treatment groups, consistent with previous findings for FF 50 mcg and FP 100 mcg (10, 18). Steroid-related AEs were not anticipated for the strengths of FF or FP used in this study (10, 27); however, there were reports of oral candidiasis with both treatments. There were no reports of pneumonia with FF, but there was a single pneumonia event in each of the FP and placebo groups. The low frequency of exacerbations was as expected for the cohort of patients studied.

The strengths of this study included the 24-week treatment period, the longest to date for FF at this dose, high levels of compliance across all treatment groups, and the inclusion of FP as a positive control. Potential limitations include the substantial placebo response for the primary endpoint and the fact that the study was not formally powered to compare FF with FP.

In conclusion, once-daily FF 50 mcg was not effective in improving trough FEV_1 in this population of patients with mild-to-moderate persistent asthma, as it did not produce a significantly greater improvement than placebo after 24 weeks. These results are inconsistent with previous findings. A statistically significant improvement was seen for the same endpoint with twice-daily FP 100 mcg. Both FF and FP were well tolerated, and no safety issues of clinical concern were identified.

Author contributions

W.W.B, E.D.B, P.M.O'B, J.L, A.W, R.F and L.J were involved in the conception and design of the study; R.F was involved in data analysis; W.W.B, E.D.B, P.M.O'B, J.L, A.W, H.M. R.F, and L.J were involved in the interpretation of data. The study was sponsored by GlaxoSmithKline. Employees of the sponsor were involved in the conception, design and conduct of the study, and in data collection and analysis. All authors, including authors employed by the sponsor, participated in the development of the manuscript and had access to the data from the study. The decision to submit for publication was that of the authors alone.

Conflicts of interest

W.W.B. has served as a consultant to Amgen, AstraZeneca, Boehringer Ingelheim, Genentech, GlaxoSmithKline, MedImmune, and Novartis; served on advisory boards for Merck Sharpe, and Dohme; and received research funding from AstraZeneca. E.D.B. has served as a consultant to AlkAbello, Almirall, Boehringer Ingelheim, Cephalon, Hoffman la Roche, ICON, and MS Consulting Group; been on advisory boards for Almirall, AstraZeneca, Boehringer Ingelheim,

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Exclusion criteria at screening and randomization.

Appendix S2. Restricted concomitant medications.

Appendix S3. Details of statistical analyses used for the 'other' endpoints.

Appendix S4. Use of concomitant medications during the study treatment period.

Appendix S5. Cumulative incidence curve of time to withdrawal due to lack of efficacy (intent-to-treat population).

Figure S1. Figure related to Appendix S5. BD, twice-daily; FF, fluticasone furoate; FP, fluticasone propionate; OD, once daily.

References

1. Fanta CH. Drug therapy: asthma. *N Engl J Med* 2009;**360**:1002–1014.
2. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention 2012. Available at: http://www.ginasthma.org/local/uploads/files/GINA_Report_March13.pdf. Last accessed 11 April 2014.
3. Demoly P, Annunziata K, Gubba E, Adamek L. Repeated cross-sectional survey of patient-reported asthma control in Europe in the past 5 years. *Eur Respir Rev* 2012;**21**:66–74.
4. Emilsson M, Berndtsson I, Lötvall J, Millqvist E, Lundgren J, Johansson Å et al. The influence of personality traits and beliefs about medicines on adherence to asthma treatment. *Prim Care Respir J* 2011;**20**:141–147.
5. Guest JF, Davie AM, Ruiz FJ, Greener MJ. Switching asthma patients to a once-daily inhaled steroid improves compliance and reduces healthcare costs. *Prim Care Respir J* 2005;**14**:88–98.
6. Price D, Robertson A, Bullen K, Rand C, Horne R, Staudinger H. Improved adherence with once-daily versus twice-daily dosing of mometasone furoate administered via a dry powder inhaler: a randomized open-label study. *BMC Pulm Med* 2010;**10**:1.
7. Cochrane GM, Horne R, Chanez P. Compliance in asthma. *Respir Med* 1999;**93**:763–769.
8. 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**:3349–3352.
9. Rossios C, To Y, Ito M, Barnes PJ, Adcock IM, Johnson M et al. Long-acting fluticasone furoate has a superior pharmacological profile to fluticasone propionate in human respiratory cells. *Eur J Pharmacol* 2011;**670**:244–251.
10. Bateman ED, Bleecker ER, Lötvall 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**:642–650.
11. Busse WW, Bleecker ER, Bateman ED, Lötvall 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.
12. 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**:353–358.
13. Busse WW, Bateman ED, Bleecker ER, Lötvall J, Woodcock A, Forth R et al. Fluticasone furoate (FF), a once-daily inhaled corticosteroid (ICS), is efficacious in patients with uncontrolled asthma across a range of treatment steps. *Am J Respir Crit Care Med* 2011;**183**:A1298.
14. Busse WW, Bateman ED, O'Byrne PM, Lötvall J, Woodcock A, Medley H et al. Efficacy and safety of once-daily (OD) fluticasone furoate (FF) 50 mcg over 24 weeks in adults and adolescents with persistent asthma. *Eur Respir J* 2013;**42**(Suppl. 57):696s.
15. National Institutes for Health (NIH). Guidelines for the diagnosis and management of asthma – expert panel report 3 2007. Available at: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf. Last accessed 11 April 2014.
16. WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended (latest) by the 59th WMA General Assembly, Seoul, Korea, October 2008. Available at: http://www.wma.net/en/30publications/10policies/b3/index.html. Last updated October 2008. Last accessed 11 April 2014.
17. International Conference on Harmonisation Tripartite Guideline: Guidance for Good Clinical Practice E6 (R1). Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf. 1996. Last accessed 11 April 2014.
18. O'Byrne PM, Woodcock A, Bleecker ER, Bateman ED, Lötvall J, Forth R et al. Efficacy and safety of once-daily fluticasone furoate (FF) 50 mcg in adults with persistent asthma. *Am J Respir Crit Care Med* 2013;**187**:A2610.
19. Boulet LP, Turcotte H, Prince P, Lemière C, Olivenstein R, Laprise C et al. Benefits of

low-dose inhaled fluticasone on airway response and inflammation in mild asthma. *Respir Med* 2009;**103**:1554–1563.

20. Kelly EA, Houtman JJ, Jarjour NN. Inflammatory changes associated with circadian variation in pulmonary function in subjects with mild asthma. *Clin Exp Allergy* 2004;**34**:227–233.

21. Lötvall J, Bleecker ER, Busse WW, O'Byrne PM, Woodcock A, Kerwin EM et al. Efficacy and safety of fluticasone furoate 100 μg once-daily in patients with persistent asthma: a 24-week placebo and active-controlled randomised trial. *Respir Med* 2014;**108**:41–49.

22. O'Byrne PM, Bleecker ER, Bateman ED, Busse WW, Woodcock A, Forth R et al. Once-daily fluticasone furoate alone or combined with vilanterol in persistent asthma. *Eur Respir J* 2014;**43**:773–782.

23. Aggarwal AN, Gupta D, Jindal SK. The relationship between FEV_1 and peak expiratory flow in patients with airways obstruction is poor. *Chest* 2006;**130**: 1454–1461.

24. Llewellin P, Sawyer G, Lewis S, Cheng S, Weatherall M, Fitzharris P et al. The relationship between FEV1 and PEF in the assessment of the severity of airways obstruction. *Respirology* 2002;**7**:333–337.

25. 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**: 719–723.

26. Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific quality of life questionnaire. *J Clin Epidemiol* 1994; **47**:81–87.

27. Dahl R, Engelstätter R, Trebas-Pietraś E, Kuna P. 24-week comparison of low-dose ciclesonide and fluticasone propionate in mild to moderate asthma. *Respir Med* 2010;**104**:1121–1130.