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 [FEV1]) than those with more severe disease (≤65% predicted FEV1) (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 FEV1) 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 controller(s) and/or short-acting beta₂-agonists (SABAs), demonstrating best FEV₁ ≥60% predicted and reversibility of ≥12% and ≥200 ml following 2–4 inhalations of salbutamol at screening were eligible. ICS or long-acting beta₂-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 FEV₁ ≥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® 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 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) FEV₁ 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 FEV₁ 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 FEV₁, 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 FEV₁, (ii) rescue-free 24-h periods,
(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 FEV₁ 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%).

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

Primary endpoint
Improvement in change from baseline in predose evening trough FEV₁ 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 FEV₁ 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 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 and White | 31 (27) | 30 (26) | 34 (30) | 95 (27) |
| African American/African Heritage | 9 (8) | 14 (12) | 9 (8) | 32 (9) |
| Other*               | 2 (2)                    | 2 (2)                           | 0                           | 4 (1)                  |
| Percent reversibility FEV₁†, % | 22.98 (11.090) | 21.49 (8.247) | 23.46 (10.459) | 22.64 (10.003) |
| Baseline characteristics, mean (SD) |                      |                                 |                             |                        |
| Prebronchodilator FEV₁ (l) | 2.475 (0.7395) | 2.653 (0.6834) | 2.582 (0.8065) | 2.571 (0.7460) |
| Percent predicted FEV₁, % | 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; FEV₁, 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.
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
evening trough FEV₁ 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 FEV₁ 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 FEV₁ 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 FEV₁ <70%) (19), as were included in the 8-week study (10). Assessment of morning trough FEV₁ 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 FEV₁ 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 FEV₁ 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 FEV₁ 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).

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.
Serious AEs
On-treatment AEs occurring in 1528 AEs (safety population)

Table 3

|                | Placebo (n = 115) | OD PM (n = 117) | FF 50 mcg | OD PM (n = 117) | FP 100 mcg | BD (n = 115) |
|----------------|-------------------|-----------------|-----------|-----------------|------------|-------------|
| **AEs**        |                   |                 |           |                 |            |             |
| On-treatment   | 64 (56)           | 56 (48)         | 59 (51)   |                 |            |             |
| treatment,    | 3 (3)             | 4 (3)           | 4 (3)     |                 |            |             |
| related*       |                   |                 |           |                 |            |             |
| On-treatment, leading | 2 (2)         | 1 (<1)          | 2 (2)     |                 |            |             |
| to withdrawal  |                   |                 |           |                 |            |             |
| 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; OD, 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 FEV₁ and PEF was seen in our study and although unusual, such poor correlation has been observed by others (23, 24). Despite changes in FEV₁ 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 PEF endpoints, the observed numerical improvements with FF significant. Although significance cannot be inferred for the FP and improvements in PEF were modest and not statistically significant. 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.

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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,
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