Dose effect of once-daily fluticasone furoate in persistent asthma: A randomized trial

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Summary
Background: This randomized, double-blind, multicenter study was designed to evaluate the efficacy of inhaled once-daily fluticasone furoate (FF) administered in the evening in patients with persistent asthma not controlled by short-acting beta2 agonists, and to determine the dose(s) suitable for further development.
Methods: Of 1459 patients screened, 598 received one of six treatments: placebo, FF (25 μg, 50 μg, 100 μg or 200 μg) once daily each evening, or fluticasone propionate (FP) 100 μg twice daily for 8 weeks. The primary endpoint was change from baseline in pre-dose evening forced expiratory volume in 1 s (FEV1).
Results: A dose–response effect was observed for once-daily FF 25–200 μg including (p < 0.001) and excluding placebo (p = 0.03). FF 50–200 μg once daily significantly increased FEV1 from baseline (p < 0.05 vs placebo), by >200 mL for FF 100 μg and 200 μg. Significant improvements were also achieved for peak expiratory flow, and percentage symptom-free and rescue-free 24 h periods. The magnitude of effect was at least as good as twice-daily FP. Overall, once-daily FF was well tolerated with no systemic corticosteroid effects.
Introduction

Inhaled corticosteroids (ICS) are the most effective anti-inflammatory treatments for all severities of persistent asthma.1–3 Their benefits include control of asthma symptoms, improved lung function, and reduced frequency of exacerbations.4–6 However, these benefits are lost when treatment is discontinued. Poor adherence is a common cause of poor asthma control.7

Strategies to improve compliance with controller therapy include combining treatments such as an ICS and a long-acting beta2 agonist (LABA) in a single inhaler,8,9 and less frequent dosing.10 Currently available ICS + LABA combinations are licensed for twice-daily dosing, but oncedaily combination regimens are being explored. Once-daily administration of controller therapy for asthma could offer greater convenience to the patient, and with this the potential for improved adherence and asthma control.11 The optimal time for once-daily dosing of an ICS is unclear. Factors such as night-time worsening of asthma symptoms and the circadian fluctuation in cortisol levels support evening dosing.12 Clinical data on this strategy are limited, but studies with once-daily budesonide, mometasone furoate, and ciclesonide suggest that evening dosing is at least as effective as morning dosing,13 or may even be more effective than morning dosing in improving peak expiratory flow (PEF)12 or forced expiratory volume in 1 s (FEV1)/forced vital capacity at the same total daily dose of ICS.14

Demonstrating a dose response to ICS for most efficacy outcomes in asthma is difficult using conventional study designs.15 In mild-to-moderate asthma, most benefit with an ICS is achieved at low doses (equivalent to <100 μg twice-daily fluticasone propionate [FP])16 and adverse effects (AEs) increase with increasing doses.17 Results from preclinical models indicate that fluticasone furoate (FF) is a novel enhanced-affinity ICS with a pharmacological profile that demonstrates greater retention in the lung, and longer duration of action than twice-daily FP.18 FF and FP have distinct chemical structures and glucocorticoid receptor binding affinities. FF has an ester derived from 2-furoic acid at the C-17a position replacing the simpler propionate ester, this results in more complete occupancy of the 17α pocket in the glucocorticoid receptor.19 This structural difference with FF results in a higher glucocorticoid receptor binding affinity than with FP.18 Early phase20 and phase IIb21,22 clinical studies support the potential for FF as a once-daily inhaled asthma control therapy with a favorable therapeutic index. In addition, FF administered once daily in the evening is as effective as the same total daily dose administered twice daily in patients with asthma, thus supporting the suitability of FF for once-daily dosing.23 FF is being co-developed with vilanterol.

trifenate (VI, GW642444M), a new LABA with inherent 24 h activity,24 in a novel dry powder inhaler (nDPI) formulation.

We evaluated the efficacy and safety of four doses of FF administered once daily in the evening in patients with persistent, uncontrolled asthma in a placebo-controlled study with FP as active control. The study was powered to demonstrate a dose–response effect on lung function (FEV1). Preliminary results from this study have been previously presented as an abstract.25

Patients and methods

Patients

Patients were aged ≥12 years with a diagnosis of persistent asthma not optimally controlled on short-acting beta2 agonists (SABA) or other non-steroidal controllers, which they had been using for ≥3 months, and a baseline FEV1 of 40%–90% of predicted normal between 17.00 h and 23.00 h (or 40%–85% between 05.00 h and 12.00 h to account for the known diurnal lung function variation in asthma patients). Patients had to demonstrate reversibility of FEV1 of at least 12% and 200 mL with salbutamol inhalation aerosol.

After 4 weeks’ run-in, patients entered the treatment period if evening pre-dose FEV1 was 40%–90% and they continued to be symptomatic (combined daily asthma symptom score ≥1 or salbutamol use on ≥4 of the last 7 days of run-in). Key exclusion criteria at enrollment and at the end of the run-in period are detailed in Supplement 1.

Study design and treatments

This was a randomized, double-blind, double-dummy, parallel-group, placebo- and active-controlled study (GSK study FFA109687; ClinicalTrials.gov NCT00603382) conducted in 142 centers in 14 countries worldwide, between 19 December 2007 and 2 October 2008 (for details see Supplementary Table 1). The study was approved by local ethics committees, and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent was obtained from each patient.

Patients who successfully completed run-in were randomized (ratio, 1:1:1:1:1:1) to one of six treatment groups: placebo, FF (25 μg, 50 μg, 100 μg, or 200 μg) once daily in the evening, or FP 100 μg twice daily (an active control for assay sensitivity and assessment of the relative magnitude of responses to FF). Patients and investigators were blinded to treatment assignment and the placebo and FF formulations were indistinguishable. Further details of
the study design, randomization schedule (RandAll) and allocation method (RAMOS) are described in Supplement 2.

Treatment duration was 8 weeks. FF was administered once daily in the evening using a nDPI, further details of which will be described in a separate publication. FP was administered twice daily via Diskus™/Accuhaler™. Placebo was administered twice daily via Diskus/Accuhaler for each FF group, every evening via the nDPI device for the FP group, and via both delivery systems for the placebo group. Assessment of appropriate device use was made at each study visit and adherence was assessed using the device dose counters. Other than as-needed salbutamol, no concomitant asthma medications were permitted during the treatment period. All other permitted medications (Supplement 1) taken were recorded.

Study visits took place at Weeks 1, 2, 4, 6, and 8 of active treatment; a follow-up clinic visit or telephonic consultation was conducted 1 week after completing study medication.

Efficacy measurements

Using the eDiary (Asthma Monitor II [AM II] electronic diary device, Cardinal Health Research Services, Hoechberg, Germany)26 and with time and date stamped, patients kept a daily record of daytime and night-time asthma symptom scores for each 24 h period (daytime symptoms scored from '0, no symptoms', to '5, symptoms so severe that patient could not go to work or perform normal daily activities'; night-time symptoms scored from '0: no symptoms', to '4: symptoms so severe that the patient did not sleep at all'), rescue salbutamol use, and morning and evening PEF measurements (pre-dose and pre-rescue bronchodilator). FEV₁ was measured before dosing with study medication at evening clinics using centralized spirometry (MasterScope CT) and according to ATS/ERS guidelines.29

The primary endpoint was mean change from baseline in pre-dose evening FEV₁ at the end of 8 weeks' treatment (with and without placebo adjustment). Secondary endpoints were mean changes from baseline in daily evening and morning PEF averaged over the 8-week treatment period; percentage of symptom-free 24 h periods during treatment; percentage of rescue-free 24 h periods; and number of withdrawals due to lack of efficacy (worsening of asthma) during treatment. Other efficacy endpoints evaluated but not reported here are shown in Supplement 3.

Safety evaluation

AEs were coded using the MedDRA dictionary (Version 11) and reported by primary System Organ Class and Preferred Term. Standard laboratory parameters (hematology, clinical chemistry, and urinalysis) and 24 h urinary cortisol (UC) excretion assessment were performed before and at the end of treatment and were analyzed at a central laboratory. Vital signs and oropharyngeal examination (for signs of oropharyngeal candidiasis; coded as oral candidiasis, oropharyngeal candidiasis, or candidiasis) were assessed at screening and at Visits 3–8.

Pharmacokinetic assessments

Blood samples for pharmacokinetic assessment of once-daily FF were collected from all patients before and after dosing at Weeks 2 and 8 of study treatment and analyzed at a central laboratory using validated methods, with a lower limit of quantification of 10 pg/mL.

Statistical analyses

A total of 594 evaluable patients were required to demonstrate a 200 mL improvement per 200 μg of FF (dose–response slope 1 mL/μg) in the primary endpoint, with 96% power and significance at the two-sided 5% level. The study had 90% power to detect a 200 mL difference in pair-wise comparisons between any active dose and placebo.

The intent-to-treat (ITT) population included all patients randomized to treatment and who received at least one dose of study medication, and constituted the primary population for all analyses of efficacy and safety measures (excluding UC analyses). The per protocol (PP) population included ITT population patients without a full protocol deviation and was used for confirmatory analyses of the primary efficacy endpoint. The UC population comprised patients whose urine samples did not have confounding factors that could affect the interpretation of results.

The primary treatment comparison was for linear dose—response in pre-dose evening FEV₁ at Week 8 across the four FF doses (with and without placebo) to demonstrate overall efficacy of FF. Each dose of FF was also compared with placebo to identify effective doses, using analysis of covariance (ANCOVA) with last observation carried forward to impute missing data. Pair-wise comparisons were performed for the other key efficacy endpoints on the ITT population, and for 24 h UC excretion on the ITT and UC populations.

Results

Study population

Of 1459 patients recruited, 598 were randomized and received at least one dose of study treatment (ITT population; Fig. 1). Demographics and baseline characteristics were similar across groups (Table 1). Mean age was 37–41 years; over half of patients had at least a 10-year history of asthma, and approximately 20% had an asthma exacerbation during the last 6 months. The most frequently taken asthma medications taken during the run-in period were salbutamol (90%–96%) and montelukast (<5%) (Supplementary Table 2). A total of 518 patients completed study treatment. Reasons for withdrawal are detailed in Supplementary Fig. 1.

Adherence to study medication was consistently high (92.4%–97.0% for the Diskus/Accuhaler; 96.0%–101.0% for the nDPI). Mean exposure to study medication was similar across the active treatment groups (51.0–54.1 days for both devices) and placebo (49.9/49.8 days).
Efficacy

A significant dose–response relationship for change in pre-dose evening FEV1 (baseline—Week 8) was achieved across once-daily FF (25–200 μg) both when placebo was included (p < 0.001) and when placebo was not included (p = 0.03; Table 2). At Week 8, all active treatment groups showed a >200 mL improvement in pre-dose FEV1 from baseline; the 100 μg and 200 μg once daily doses achieved a >200 mL difference compared with placebo (p < 0.001). FF 50 μg once daily, although failing to reach the pre-defined 200 mL difference, was also significantly better than placebo (p < 0.05), but superiority vs placebo was not demonstrated for FF 25 μg once-daily or for FP 100 μg twice-daily (Fig. 2). Similar results were shown in the PP population, except that FF 25 μg once-daily also achieved significance (data not shown).

In the secondary endpoint analyses, evening PEF improvements from baseline were largest in the FF 50 μg and 200 μg once-daily groups (mean difference 20.7 and 21.7 L/min, respectively, vs placebo; p < 0.001). Significant but smaller differences were also achieved with FF 25 μg once daily (14.0 L/min, p = 0.019) and 100 μg once daily (16.1 L/min, p = 0.005) and were of a similar magnitude to FP 100 μg twice-daily (14.9 L/min; p = 0.011). Similarly, all active treatment groups improved morning PEF relative to baseline (Fig. 3) and these changes were significantly greater than with placebo; FF 200 μg once daily exhibited the greatest difference (22.0 L/min; p < 0.001).

Trends in the percentage of 24 h periods that were symptom-free or rescue-free are shown in Figs. 4 and 5, respectively. For symptom-free periods, FF 100 μg once daily demonstrated the greatest increase from baseline relative to placebo (20.2%). FF 50 μg and 200 μg once daily showed numerically lower increases, similar in magnitude to the FP 100 μg twice-daily group. For all except the FF 25 μg once-daily group, the effect was significantly better than for placebo. A similar pattern was evident for rescue-free periods.

Withdrawal rates due to lack of efficacy were highest in the placebo and FP twice-daily groups (15% and 11%, respectively; Fig. 1). Rates for FF once-daily ranged from 3% to 9%, and for the 50 μg (3%) and 100 μg (5%) once-daily groups were significantly lower than for placebo (p = 0.004 and p = 0.032, respectively).

Safety

Overall, 26%, 34%, and 20–32% of patients in the placebo, FP twice-daily and FF once-daily groups, respectively,
### Table 1  Demographics and baseline characteristics (ITT population).

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Fluticasone furoate</th>
<th>Fluticasone propionate</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>25 µg OD</td>
<td>50 µg OD</td>
<td>100 µg OD</td>
</tr>
<tr>
<td><strong>Patients, n</strong></td>
<td>94</td>
<td>97</td>
<td>100</td>
</tr>
<tr>
<td><strong>Age, mean (range)</strong></td>
<td>39.2 (12–78)</td>
<td>37.7 (13–69)</td>
<td>38.3 (12–65)</td>
</tr>
<tr>
<td><strong>Females, n (%)</strong></td>
<td>47 (50)</td>
<td>57 (59)</td>
<td>59 (59)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>69 (73)</td>
<td>64 (66)</td>
<td>72 (72)</td>
</tr>
<tr>
<td>African American/African</td>
<td>5 (5)</td>
<td>4 (4)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Asian</td>
<td>7 (7)</td>
<td>13 (13)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Other/mixed race</td>
<td>13 (14)</td>
<td>16 (16)</td>
<td>15 (15)</td>
</tr>
<tr>
<td><strong>Duration of asthma, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6 months to &lt;5 years</td>
<td>16 (17)</td>
<td>19 (20)</td>
<td>20 (20)</td>
</tr>
<tr>
<td>5 years to &lt;10 years</td>
<td>13 (14)</td>
<td>20 (21)</td>
<td>15 (15)</td>
</tr>
<tr>
<td>≥10 years</td>
<td>65 (69)</td>
<td>58 (60)</td>
<td>65 (65)</td>
</tr>
<tr>
<td>History of atopy, n (%)</td>
<td>45 (48)</td>
<td>38 (39)</td>
<td>50 (50)</td>
</tr>
<tr>
<td>Exacerbations (≥1) in previous 6 months, n (%)</td>
<td>20 (21)</td>
<td>17 (18)</td>
<td>19 (19)</td>
</tr>
</tbody>
</table>

**Lung function**

**FEV₁ at screening, mean**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Fluticasone furoate</th>
<th>Fluticasone propionate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.320</td>
<td>2.394</td>
<td>2.335</td>
</tr>
<tr>
<td>Pre-bronchodilator (L)</td>
<td>67.03</td>
<td>69.69</td>
<td>69.20</td>
</tr>
<tr>
<td>Pre-bronchodilator (% predicted)</td>
<td>28.09</td>
<td>26.43</td>
<td>29.84</td>
</tr>
</tbody>
</table>

**FEV₁ at baseline, mean (L)**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Fluticasone furoate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.373</td>
<td>2.456</td>
</tr>
</tbody>
</table>

**Daily diary data at baseline, mean**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Fluticasone furoate</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM PEF (L)</td>
<td>355.4</td>
<td>370.8</td>
</tr>
<tr>
<td>AM PEF (L)</td>
<td>342.7</td>
<td>359.0</td>
</tr>
<tr>
<td>Rescue-free 24 h periods (%)</td>
<td>10.5</td>
<td>9.5</td>
</tr>
<tr>
<td>Symptom-free 24 h periods (%)</td>
<td>13.5</td>
<td>11.0</td>
</tr>
</tbody>
</table>

BD: twice daily; FEV₁: forced expiratory volume in 1 s; FP: fluticasone propionate; OD: once daily; PEF: peak expiratory flow.

a Baseline defined as start of randomization period (Visit 3).

### Table 2  Linear trend test and statistical analysis of change from baseline in pre-dose (trough) FEV₁ at Week 8 (ITT population).

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>FF</th>
<th>FP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25 µg OD</td>
<td>50 µg OD</td>
<td>100 µg OD</td>
</tr>
<tr>
<td><strong>Patients, n</strong></td>
<td>93</td>
<td>94</td>
<td>97</td>
</tr>
<tr>
<td><strong>Trough FEV₁ (L)</strong></td>
<td>2.515</td>
<td>2.617</td>
<td>2.644</td>
</tr>
<tr>
<td>LS mean (Week 8)</td>
<td>0.137</td>
<td>0.239</td>
<td>0.266</td>
</tr>
<tr>
<td><strong>Difference vs placebo</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LS difference</td>
<td>0.101</td>
<td>0.129</td>
<td>0.204</td>
</tr>
<tr>
<td>95% CI</td>
<td>-0.018, 0.221</td>
<td>0.011, 0.247</td>
<td>0.089, 0.319</td>
</tr>
<tr>
<td>p value (vs placebo)</td>
<td>0.095</td>
<td>0.033</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Linear trend, FF and placebo</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p value (excluding placebo)</td>
<td>&lt;0.001</td>
<td>0.030</td>
<td>0.711</td>
</tr>
<tr>
<td>Slope (mL/µg)</td>
<td>1.016</td>
<td>0.711</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>(0.472, 1.559)</td>
<td>(0.069, 1.354)</td>
<td></td>
</tr>
</tbody>
</table>

BD: twice daily; CI: confidence interval; FEV₁: forced expiratory volume in 1 s; FF: fluticasone furoate; FP: fluticasone propionate; LS: least squares; OD: once daily.
reported at least one on-treatment AE (Table 3). AEs considered drug-related were low in all groups (FF 25 \( \mu \)g, 0%; to FP, 6%), with no apparent dose-dependent events. Six serious AEs occurred in four patients; none were considered to be study medication related: snake bite (FF 25 \( \mu \)g; patient discontinued study treatment); depression (FF 100 \( \mu \)g); gastritis (FP); and chest pain, hyperhidrosis and hypertension (FP; discontinued study). Five further withdrawals were linked with (non-serious) AEs: FF 50 \( \mu \)g (n = 1), FF 100 \( \mu \)g (n = 2), FF 200 \( \mu \)g (n = 1) once daily and FP 100 \( \mu \)g twice daily (n = 1). There were no deaths or hospitalizations associated with AEs.

Asthma exacerbations (defined as worsening asthma requiring any treatment other than study medication or rescue salbutamol alone) occurred in seven patients and necessitated study withdrawal: FF 25 \( \mu \)g (n = 1), FF 100 \( \mu \)g (n = 3), FF 200 \( \mu \)g (n = 1) and FP (n = 2). Three patients in the FF 100 \( \mu \)g once-daily group and two patients in the FP 100 \( \mu \)g twice-daily group required oral corticosteroids but none required hospitalization. The primary cause of most exacerbations was an upper respiratory tract infection and two patients (FF 200 \( \mu \)g; FP) cited lack of efficacy. The incidence of on-treatment oropharyngeal candidiasis was low across all groups: FF 25 \( \mu \)g, 0%; FF 50—200 \( \mu \)g, 2%—4%; FP, <1%; and placebo, 0%.

Pharmacokinetic analysis

Of 1456 evaluable samples in 381 patients (94.8% of the FF ITT population), 71.0% were below the lower limit of quantification (10 pg/mL) for FF. The number of patients reporting at least one measurable value increased with dose level; however, the low number of quantifiable results did not permit a formal pharmacokinetic analysis, but confirmed low systemic exposure.
The results of this study show that 8 weeks’ treatment with FF at doses ranging from 25 to 200 μg, administered once daily in the evening, provided significant, dose-dependent improvements in the primary endpoint of pre-dose (trough) evening FEV<sub>1</sub>, including significant improvements over placebo at dose levels of 50 μg and greater. This, together with improvements in secondary endpoints and its favorable safety profile, support the benefit that this new ICS can offer to patients with asthma.

This study, in a large patient cohort, was designed to include patients who required a step-up to Step 2 of asthma treatment guidelines, i.e. with asthma not controlled on as-needed SABA alone; patients with an asthma exacerbation within 3 months of visit 1 were excluded as this study sought to identify the lowest potential dose of FF for step-up therapy. The principal comparison was once-daily FF vs placebo. FP 100 μg twice daily, a standard low-dose ICS at Step 2, was included as an active control to permit an assessment of assay sensitivity and comparison with once-daily FF responses. This study was not powered for a formal comparison between FF and FP but rather sought to evaluate whether a dose response in change from baseline lung function can be demonstrated with once-daily FF. For this reason, we selected as the primary endpoint pre-dose (trough) evening FEV<sub>1</sub>, which meant FEV<sub>1</sub> was measured 24 h after the last dose of FF and 12 h after the last dose of FP. While the magnitude of effect with all once-daily FF doses >50 μg was numerically higher than that achieved with twice-daily FP, FP did not demonstrate superiority to placebo in FEV<sub>1</sub> change from baseline over the 8 weeks of the study. This differed from findings in studies identical in design to this one conducted in patients with more severe asthma uncontrolled by low or moderate-dose ICS where FP dosed at 250 μg twice daily significantly improved lung function. Of note in those studies, the placebo response was ~65 mL<sup>21</sup> and ~43 mL<sup>22</sup> compared with the ~137 mL observed in this study. In a previous 12-week study of FP dosed at 100 μg or 200 μg in ICS-naïve asthma patients FEV<sub>1</sub> was improved by 270 mL and 110 mL, respectively, compared with an 80 mL decline in the placebo group<sup>30,31</sup>. These findings suggest that the lack of efficacy observed with FP 100 μg twice-daily in this study resulted from the high placebo response, rather than a lack of efficacy with FP per se. There are a number of possible explanations for the high placebo response. First, it is possible that inclusion into a clinical trial resulted in all patients increasing their use of rescue therapy, which was maintained in the placebo group, but as shown, was significantly reduced by active treatment (Fig. 5). Secondly, the significantly higher withdrawal rate in the placebo group, relative to active treatment, will have resulted in a ‘healthy survivor’ effect, resulting in a subset of patients in the placebo group with better lung function contributing more data to the final analysis than those withdrawn due to poorer lung function. Finally, FEV<sub>1</sub> was measured at the trough of FF dosing in the evening and it is possible that the natural diurnal variation seen in asthma lung function may have contributed to higher than expected FEV<sub>1</sub> measurements. Over 8 weeks, significant improvements in evening PEF were observed, despite the variability of the data. It is conceivable that the increase in PEF observed in the
placebo group toward the end of the study period (Fig. 3) was also consequent to the 'healthy survivor' effect.

We did not compare once-daily with twice-daily dosing of FF in our study. However, another study of FF in asthma did and showed non-inferiority of once-daily FF administered in the evening (200 µg) compared with FF administered twice daily (100 µg, morning and evening), thereby supporting suitability of FF for once-daily dosing. A goal of this study was to determine the optimal once-daily dose of FF. In the past, demonstrating a dose–response relationship for ICS in patients with mild-to-moderate asthma has proved difficult because of the relatively flat dose–response curve for FEV1, and other endpoints used to measure efficacy. Furthermore, most of the benefit of an ICS treatment is observed at doses equivalent to < 100 µg of FF twice daily. An important factor that contributed to the success of this study was the exclusion of patients who had recently used or were currently using ICS. Another important factor was the selection of FF doses. Based on the efficacy and safety profiles demonstrated in earlier clinical studies (GSK data on file), it was anticipated that the 100 and 200 µg doses would be the most effective doses. The lowest dose (25 µg) was expected to have minimal if any efficacy, but permitted a more thorough evaluation of the dose–response effects of FF. Overall, FF was well tolerated, and there was no evidence of dose-related AEs. A lack of systemic effect with once-daily FF was supported by the absence of reduced 24 h UC, a result consistent with low levels of FF detected in pharmacokinetic samples. Although a small number of asthma exacerbations were reported, this outcome cannot be adequately assessed in an 8-week study. Furthermore, the protocol defined that patients were withdrawn at the first signs of worsening asthma. Limitations of the study included the high placebo response, which may have been influenced by the strict withdrawal criteria that excluded patients who were deteriorating.

The need for improved interventions for patients with uncontrolled asthma is highlighted by the huge economic burden associated with this patient population. A cost-of-illness study in Italy found that half of the total economic burden was due to a limited proportion of poorly controlled patients. Current efforts to address this burden focus not only on development of new drugs, but also on strategies to improve adherence to controller therapy and to optimize efficacy/safety ratios through better understanding of dose–response relationships, and finally dosing strategies such as once-daily dosing.

There is evidence that evening dosing with ICS could achieve better asthma control than morning dosing. Yet, despite the known diurnal variation in asthma, few studies have directly compared morning vs evening dosing of ICS. Evening dosing with mometasone furoate DPI was superior to morning dosing in a double-blind, randomized, placebo-controlled study in patients previously on regular ICS. However, another double-blind, randomized study concluded that morning and evening dosing of ciclesonide were equally effective, with the exception of morning PEF which was higher with evening dosing. Similarly, in another study with FF, evening dosing of once-daily FF was as effective (measured as change from baseline in trough FEV1) as once-daily dosing in the morning.

In conclusion, FF administered once daily in the evening led to dose-related efficacy at doses of 50–200 µg/day and was well tolerated in asthma patients symptomatic on non-steroidal asthma therapy. FF 100–200 µg produced the greatest improvement in efficacy, without evidence of safety or tolerability concerns, and supports further evaluation as a monotherapy and in combination with a LABA in patients whose disease severity requires treatment with ICS/LABA.

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Supplementary material

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Support statement

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Competing interests

E.D.B. has served as a consultant to and received lecture fees from GlaxoSmithKline; and his institution has received remuneration for participation in clinical trials sponsored by GlaxoSmithKline. E.R.B. has served as a consultant to GlaxoSmithKline; and has performed clinical trials for GlaxoSmithKline, which have been administered by his employer Wake Forest University Health Sciences. W.W.B. has served as a consultant to AstraZeneca, Boehringer Ingelheim, 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, Cepion, GlaxoSmithKline, MedImmune and Novartis. J.L. 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 the ERS and the AAAAAI; and has participated in clinical research studies sponsored by AstraZeneca, GlaxoSmithKline, Merck Sharp and Dohme, and Novartis. A.W. has served as consultant to Almirall, AstraZeneca, Chiesi, GlaxoSmithKline, Merck Sharp and Dohme, Novartis and Schering Plough; and has received research grants and travel expenses for attendance at ATS and ERS meetings from GlaxoSmith-Kline. R.F., H.M., A.M.D, L.J. and B.H. are employees of and hold stock in GlaxoSmithKline.

References