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Efficacy and safety of fluticasone propionate/formoterol fumarate in pediatric asthma patients: a randomized controlled trial

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Abstract

Background: The efficacy and safety of fluticasone propionate/formoterol fumarate pressurized metered-dose inhaler (pMDI) (fluticasone/formoterol; Flutiform®; 100/10 μg b.i.d.) was compared with fluticasone propionate (Flixotide® Evohaler® pMDI; 100 μg b.i.d.) and fluticasone/salmeterol (Seretide® Evohaler® pMDI; 100/50 μg b.i.d.) in a pediatric asthma population (EudraCT number: 2010-024635-16).

Methods: A double-blind, double-dummy, parallel group, multicenter study. Patients, aged 5–<12 years with persistent asthma ⩾ 6 months and forced expiratory volume in 1 s (FEV_1) ⩽ 90% predicted were randomized 1:1:1 to 12 weeks' treatment. The study objectives were to demonstrate superiority of fluticasone/formoterol to fluticasone and non-inferiority to fluticasone/salmeterol.

Results: A total of 512 patients were randomized: fluticasone/formoterol, 169; fluticasone, 173; fluticasone/salmeterol, 170. Fluticasone/formoterol was superior to fluticasone for the primary endpoint: change from predose FEV_1 at baseline to 2 h postdose FEV_1 over 12 weeks [least squares (LS) mean difference 0.07 l; 95% confidence interval (CI) 0.03, 0.11; $p < 0.001$] and the first key secondary endpoint, FEV_1 area under the curve over 4 hours ($AUC_{0-4\,h}$) at week 12 (LS mean difference 0.09 l; 95% CI: 0.04, 0.13; $p < 0.001$). Per a prespecified non-inferiority margin of −0.1 l, fluticasone/formoterol was non-inferior to fluticasone/salmeterol for the primary endpoint (LS mean difference 0.00 l; 95% CI −0.04, 0.04; $p < 0.001$) and first key secondary endpoint (LS mean difference 0.01; 95% CI −0.03, 0.06; $p < 0.001$). Fluticasone/formoterol was non-inferior to fluticasone/salmeterol for the second key secondary endpoint, change from predose FEV_1 over 12 weeks (treatment difference −0.02 l; 95% CI −0.06, 0.02; $p < 0.001$), but was not superior to fluticasone for this endpoint (LS mean difference 0.03 l; 95% CI −0.01, 0.07; $p = 0.091$). All treatments elicited large improvements from baseline to week 12 for the Pediatric Asthma Quality of Life Questionnaire (LS mean change 0.76 to 0.85 units) and Asthma Control Questionnaire (LS mean change −1.03 to −1.13 units). Few severe exacerbations were seen (fluticasone/formoterol: two; fluticasone/salmeterol: two). All treatments were well tolerated.

Conclusions: This study supports the efficacy and safety of fluticasone/formoterol in a pediatric asthma population and its superiority to fluticasone.

Keywords: asthma, children, combination therapy, fluticasone propionate, formoterol fumarate, ICS/LABA

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Introduction

Inhaled corticosteroid (ICS) and long-acting β_2-agonist (LABA) combinations are recommended as a Step 3 controller option in children aged 6–11 years in the Global Initiative for Asthma (GINA) guidelines,[1] where asthma is uncontrolled on ICS alone, although the preferred step-up therapy in this age group is medium-dose ICS.

Single-inhaler combination ICS/LABA therapy has been shown to increase treatment adherence and may improve treatment outcomes compared with free combinations of ICS and LABA as it assures concomitant administration of ICS.[2–4] To date, only two ICS/LABA combination therapies are available for use in children, namely fluticasone/salmeterol as both a dry powder inhaler (DPI) and pressurized metered-dose inhaler (pMDI) (Seretide® Accuhaler®/Evohaler®, respectively) and budesonide/formoterol DPI (Symbicort® Turbohaler®).

Fluticasone propionate is an effective, well-established ICS, providing sustained anti-inflammatory effects. Formoterol fumarate is the most rapid-acting LABA, with a speed of onset comparable to the short-acting β_2-agonist, salbutamol. Flutiform®, fluticasone propionate and formoterol fumarate (fluticasone/formoterol) combination therapy *via* an HFA-propelled pMDI, has been evaluated in a number of studies in adults and/or adolescents with mild to severe asthma,[5–14] and has been approved for use in this population in over 30 countries in Europe, Asia, and elsewhere. A single open-label study has also been conducted in pediatric asthmatic patients.[15] The present study (FFLAIR: Fluticasone propionate/FormoteroL Assessed In pediatric asthma) was designed to further evaluate the efficacy and safety of fluticasone/formoterol in the pediatric population (EudraCT number: 2010-024635-16).

Methods

Participants

Male and female patients, aged 5 to <12 years, with persistent asthma for ⩾6 months, on a stable ICS dose for ⩾4 weeks, with predose forced expiratory volume in 1 s (FEV_1) ⩾ 60% to ⩽90% predicted, ⩾15% FEV_1 reversibility, and inadequate asthma control on an ICS alone at a dose of ⩽500 μg/day fluticasone (or equivalent) or controlled asthma on an ICS/LABA combination at an ICS dose of ⩽200 μg/day fluticasone (or equivalent), were eligible for enrolment.

Exclusion criteria were specified to ensure patient safety, for example, by excluding patients with potentially brittle asthma evidenced by life-threatening asthma within the past year, hospitalization or an emergency room visit for asthma within the past 6 months, systemic (injectable or oral) corticosteroid medication within 1 month and by excluding patients with current or prior nonresponse or partial response only to an ICS/LABA combination. Exclusion criteria were also specified to ensure disease stability at study entry, for example, by excluding patients with a clinically significant upper or lower respiratory infection within 4 weeks prior to study entry. Patients with coexistent pulmonary diseases (e.g. cystic fibrosis, bronchiectasis, tuberculosis) were also excluded.

Study design

This was a multicenter, randomized, double-blind, parallel-group study. Eligible patients entered a 14-day run-in period during which they received fluticasone pMDI (Flixotide® Evohaler®, GlaxoSmithKline, UK) 100 μg twice daily (b.i.d.). Salbutamol pMDI (Ventolin® Evohaler®, GlaxoSmithKline, UK) 100 μg was used as rescue medication. Patients completed an electronic diary daily to record rescue medication use, study medication use, asthma symptom scores, sleep disturbance due to asthma, and morning and evening peak flow (PEFR). The daytime and night-time symptom scales used are nonvalidated but have been employed in multiple prior studies.[5–15] Peak flow manoeuvres were performed in triplicate each morning and evening with the maximum value obtained used in subsequent analyses. Asthma symptoms were scored from 0 (no symptoms) to 5 (asthma so severe you cannot carry out normal daily activities). Sleep disturbance was scored from 0 (slept through the night, no asthma) to 4 (could not sleep at all due to asthma). An asthma control day was defined as a day with no asthma symptoms, no sleep disturbance due to asthma, and no rescue medication use. Mild to moderate asthma exacerbations were defined as at least 2 consecutive days with predose morning PEFR > 30% below baseline, and/or awakening due to asthma, and/or ⩾4 inhalations of rescue medication/day. Severe asthma exacerbations were defined as a deterioration in asthma requiring additional therapy (e.g. systemic corticosteroids) and/or

emergency room visit or hospitalization, as derived from the American Thoracic Society (ATS)/ European Respiratory Society (ERS) definitions.[16]

At the end of the run-in period, patients underwent pre- and 2 h postdose spirometry [FEV_1, forced vital capacity (FVC), forced expiratory flow at 25%, 50%, and 75% of FVC (FEF_{25}, FEF_{50}, FEF_{75} and $FEF_{25–75}$) and PEFR] and 4 h serial spirometry [FEV_1 area under the curve over 4 h ($AUC_{0–4\ h}$)] performed in accordance with ATS/ERS standards[17] (and subjected to centralized over-reading), asthma control (ACQ) and health status (Pediatric Asthma Quality of Life; PAQLQ) questionnaires were completed, a 12 h overnight urine collection was performed and, in a subgroup of patients, fractional exhaled nitric oxide (FeNO) was assessed. Patients were included in this subgroup based on the availability of FeNO equipment at site.

At the end of the run-in period, only patients fulfilling the following criteria were eligible for randomization: $FEV_1 \leqslant 90\%$ predicted (following appropriate withholding of study medication) *and*, during the last 7 days of the run-in period, rescue medication use for at least 3 days *and* at least one night with sleep disturbance (i.e. sleep disturbance score of $\geqslant 1$) *and/or* at least 3 days with asthma symptoms (i.e. a symptom score of $\geqslant 1$). Note that the run-in period could be extended to 28 days if a patient failed to meet the randomization criteria after the initial 14-day period.

Eligible patients were randomized 1:1:1 to one of three treatment groups: fluticasone pMDI (Flixotide Evohaler) 100 μg b.i.d., fluticasone/formoterol pMDI [Flutiform] 100/10 μg b.i.d. or fluticasone/salmeterol pMDI [Seretide Evohaler] 100/50 μg b.i.d. Randomization was performed by the study sponsor using a validated system that automates the random assignment of treatment groups to randomization numbers, and was stratified to ensure balanced allocation within the age groups 5 to <8 years and 8 to <12 years.

Patients received study medication for 12 weeks.

All patients received two inhalers during the treatment period: active or placebo fluticasone and a corresponding active or placebo ICS/LABA (fluticasone/formoterol or fluticasone/salmeterol). Thus, allocation to ICS or ICS/LABA was fully blinded, whilst *potential* allocation to fluticasone/formoterol or fluticasone/salmeterol was open label.

During the treatment period, patients attended four clinic visits (at weeks 1, 4, 8, 12) and completed their electronic diaries throughout the treatment period. Pre- and 2 h postdose lung function was assessed at each clinic visit. At week 12, 4 h serial spirometry was performed, a 12 h (overnight) urine collection was gathered (commencing the evening prior to the final clinic visit), ACQ and PAQLQ were completed, and FeNO was again assessed in a subgroup. The occurrence of adverse events (AEs) was monitored throughout the study whilst routine hematology and biochemistry were performed at screening and week 12. A 14-day follow-up period concluded the study (Figure 1).

The study was performed in accordance with the Declaration of Helsinki, the International Council for Harmonization Harmonized Tripartite Guidelines for Good Clinical Practice, and approved by independent ethics committees (Table S1). All patients and their guardians/legally authorized representatives were provided with oral and written information describing the study. The patient's guardian/legally authorized representative signed an informed consent form.

The primary endpoint was the change from predose FEV_1 at baseline (day 1) to 2 h postdose FEV_1 over the 12-week treatment period. The first key secondary endpoint was FEV_1 $AUC_{0–4h}$ at week 12. The second key secondary endpoint was the change from predose FEV_1 at baseline to predose FEV_1 over the 12-week treatment period. These endpoints were selected on the basis of regulatory guidelines, following discussions with national regulatory authorities and the European Medicines Agency's Pediatric Committee, and on the basis of the predictive value of pre- and postdose lung function for future exacerbation risk.[16,18–21]

Statistics

The sample size of 159 patients per group was based on an estimated difference between fluticasone/formoterol and fluticasone (the primary comparison) for the primary endpoint of 100 ml[8,22,23] assuming a standard deviation of 274 ml,[15] 90% power, and a two-sided alpha (α) of 0.05.

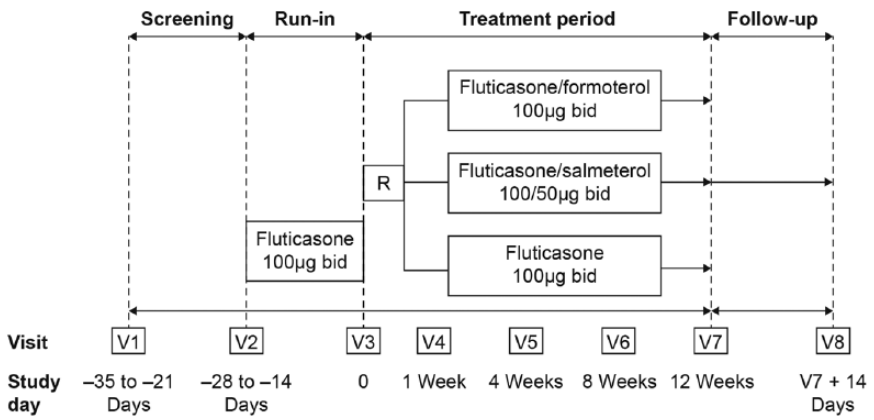

Figure 1. Study design.
b.i.d., twice daily; R, randomization; V, visit.

The full analysis population (FAP) included all randomized patients who received at least one dose of study medication and had at least one valid efficacy (FEV_1) assessment. The per protocol population (PPP) included all patients in the FAP without major protocol violations.

The primary and key secondary endpoints were analyzed using a repeated measures approach based on observed data. For these endpoints, the primary comparison between fluticasone/formoterol and fluticasone was tested for superiority, based on the FAP. The secondary comparison (fluticasone/formoterol *versus* fluticasone/salmeterol) was tested for non-inferiority, based on the PPP. Non-inferiority was concluded if the lower limit of the 95% confidence interval (CI) for the least squares (LS) mean difference between treatments was $\geqslant -0.1$ l. Supportive analyses for each comparison were performed using the alternative population. To account for missing data, sensitivity analyses were performed using multiple imputation methods.

The primary endpoint was tested in a hierarchical (gate keeping) manner. The test procedure started with the fluticasone/formoterol *versus* fluticasone comparison (evaluating superiority) and continued to the fluticasone/formoterol *versus* fluticasone/salmeterol comparison (evaluating non-inferiority) in a confirmatory manner, only if the first comparison (fluticasone/formoterol *versus* fluticasone) was significant at the 0.05 α level. If both 2 h postdose FEV_1 comparisons were significant at the 0.05 α level (i.e. showed superiority compared with fluticasone and non-inferiority compared with fluticasone/salmeterol), only then were the key secondary endpoints (FEV_1 AUC at week 12 and change in predose FEV_1 over 12 weeks) tested in pairs using a Hochberg closed-testing procedure. The treatment comparisons were therefore ordered, such that if the comparison with the larger p value was not significant at $\alpha = 0.05$, but the lower p value was significant at $\alpha = 0.025$, the treatment comparison associated with the lower p value was considered statistically significant. Only if both treatment comparisons of the first pair of secondary endpoints (i.e. for FEV_1 AUC_{0-4h}) were significant at the $\alpha = 0.05$ level, would the next pair of secondary endpoints (i.e. for change in predose FEV_1) be tested in a confirmatory manner. Therefore, p values would be considered confirmatory if observed as statistically significant in the hierarchical testing strategy. If the confirmatory testing was stopped, subsequent endpoints in the hierarchy, as with the statistical tests of all other endpoints, would be considered exploratory.

The primary endpoint was analyzed using a repeated-measures analysis of covariance (ANCOVA) with fixed terms for treatment, age group, predose FEV_1 at baseline, visit and treatment by visit interaction, and center as a random effect. A similar model was employed to analyse the second key secondary endpoint (change in predose FEV_1 from baseline over 12 weeks). FEV_1 $AUC_{0-4\,h}$ at week 12 was analyzed using an ANCOVA with fixed terms for treatment, age group, predose FEV_1 at baseline, and center as a random effect.

For other efficacy endpoints, both treatment comparisons (fluticasone/formoterol *versus* fluticasone,

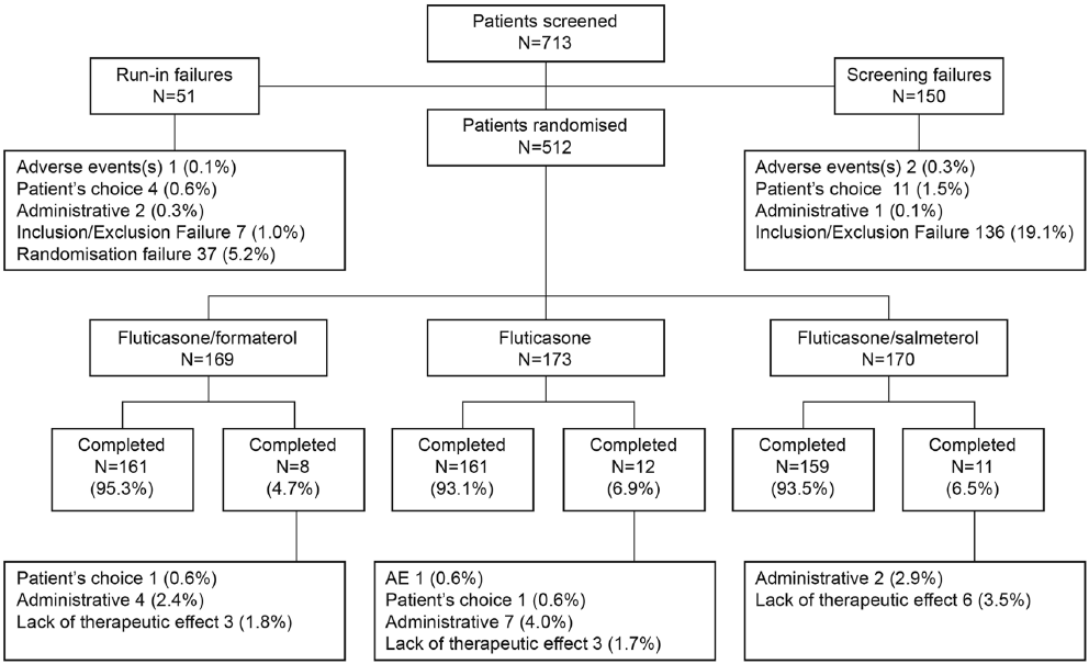

Figure 2. Patient flow diagram.

fluticasone/formoterol *versus* fluticasone/salmeterol) were tested for superiority and based on the FAP (unless otherwise stated) in an exploratory manner.

Change from baseline in diary morning and evening predose PEFR, asthma symptom scores, sleep disturbance scores, percentage of symptom-free days, percentage of awakening-free nights, percentage of rescue-medication-free days, percentage of asthma-control days were analyzed using a similar repeated-measures ANCOVA as per the primary endpoint. The change in FeNO from baseline, PAQLQ and ACQ scores were analyzed using an ANCOVA as per FEV_1 $AUC_{0–4\,h}$.

Post hoc analyses of the change from baseline in diary morning and evening predose FEV_1 over 12 weeks were performed using a similar repeated-measures ANCOVA as per the primary endpoint. *Post hoc* analyses of the change in clinic PEFR from predose at baseline to predose over the 12-week treatment period, and from predose at baseline to 2 h postdose over the 12-week treatment period were also performed using a similar ANCOVA to that employed for the primary endpoint analysis [but with predose PEFR (rather than FEV_1) at baseline as a fixed term].

The incidence of asthma exacerbations, the incidence of discontinuations due to lack of efficacy, the proportion of patients achieving a PAQLQ score increase $\geqslant$ 0.5 units, and the proportion of patients achieving an ACQ score reduction $\geqslant$ 0.5 units were analyzed using logistic regression. The annualized rate of asthma exacerbations was analyzed using a negative binomial model. The time to first asthma exacerbation was analyzed using a Cox proportional hazards model. The change in rescue medication puffs per day from baseline to each subsequent visit over the 12-week treatment period was analyzed using a repeated measures Friedman test. Other endpoints were summarized descriptively.

The analysis of safety data was based on the safety population, that is, all randomized patients who received at least one dose of study medication. Only descriptive summaries were generated.

Results

A total of 713 patients were screened and 512 randomized at 59 centers in 8 countries (Bulgaria, Czech Republic, Hungary, India, Poland, Romania, Russia and Ukraine). Of these, 481 patients (93.9%) completed the study. Slightly fewer patients discontinued in the fluticasone/formoterol group (8 patients) compared with the other treatment groups (fluticasone/salmeterol: 11; fluticasone: 12; Figure 2).

Table 1. Demography and asthma characteristics at screening, full analysis population.

		Fluticasone/ formoterol	Fluticasone	Fluticasone/ salmeterol	Total
		(*n* = 167)	**(*n* = 171)**	**(*n* = 168)**	**(*n* = 506)**
Age (years)	Mean (SD)	8.4 (1.81)	8.4 (1.86)	8.6 (1.80)	8.5 (1.82)
Gender (*n*)	Male/female	109/58	116/55	113/55	338/168
Race [*n* (%)]	Caucasian	164 (98.2)	167 (97.7)	165 (98.2)	496 (98.0)
	Asian	3 (1.8)	4 (2.3)	3 (1.8)	10 (2.0)
Duration of asthma (years)	Mean (SD)	3.5 (2.36)	3.8 (2.50)	3.5 (2.43)	3.6 (2.43)
		(*n* = 166)	**(*n* = 167)**	**(*n* = 166)**	**(*n* = 499)**
FEV_1 presalbutamol (l)	Mean (SD)	1.48 (0.361)	1.44 (0.354)	1.50 (0.360)	1.47 (0.358)
% Predicted FEV_1	Mean (SD)	73.8 (6.76)	72.1 (7.17)	73.5 (7.63)	73.1 (7.22)
FEV_1 reversibility (%)	Mean (SD)	24.1 (10.49)	26.1 (11.49)	24.9 (9.75)	25.0 (10.62)
Patients using ICS alone	*n* (%)	118 (70.7)	132 (77.2)	129 (76.8)	379 (74.9)
Median daily ICS dose	μg (min, max)	200.0 (37.5, 500.0)	200.0 (50.0, 500.0)	200.0 (50.0, 500.0)	200.0 (37.5, 500.0)
Patients using ICS and LABA	*n* (%)	49 (29.3)	39 (22.8)	39 (23.2)	127 (25.1)

FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; SD, standard deviation.

Demographic and baseline asthma characteristics of all three treatment groups were similar (Table 1).

Primary endpoint

Fluticasone/formoterol was superior to fluticasone for the change from predose FEV_1 at baseline to 2 h post dose FEV_1 over the 12-week treatment period. The LS mean difference (fluticasone/formoterol *versus* fluticasone) was 0.07 l [95% CI: 0.03, 0.11 l, $p < 0.001$ (FAP)] (Figure 3). Fluticasone/formoterol was non-inferior to fluticasone/salmeterol per the pre-specified non-inferiority margin of −0.1 l: LS mean difference 0.00 l [95% CI: −0.04, 0.04 l, $p < 0.001$ (PPP)]. Very similar results were obtained for the alternate populations (PPP and FAP) and for the sensitivity analyses for both treatment comparisons.

Key secondary endpoints

Forced expiratory volume in 1 s area under the curve over 4 h at week 12. Fluticasone/formoterol was superior to fluticasone with regards to FEV_1 AUC_{0-4h} at week 12. The LS mean treatment difference (fluticasone/formoterol *versus* fluticasone) was 0.09 l [95% CI: 0.04, 0.13 l, $p < 0.001$ (FAP)] (Figure 4). Fluticasone/formoterol was non-inferior to fluticasone/salmeterol per the pre-specified non-inferiority margin of −0.1 l: LS mean difference 0.01 l [95% CI: −0.03, 0.06, $p < 0.001$ (PPP)]. Similar results were obtained for the alternate populations (PPP and FAP) for both treatment comparisons.

Change in predose area under the curve over 4 h from baseline over 12-week treatment period. A numerically greater effect was seen with fluticasone/formoterol compared with fluticasone, but

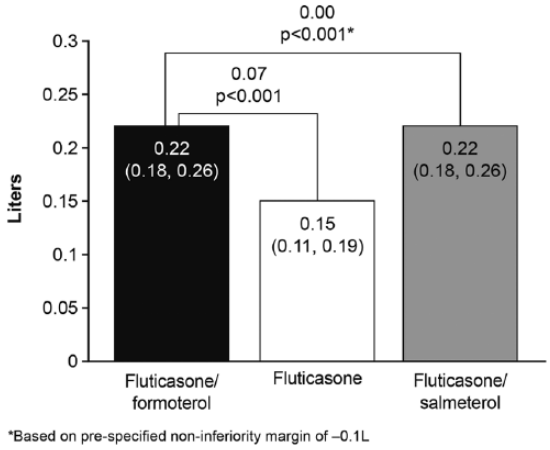

Figure 3. Least squares mean change from predose forced expiratory volume in 1 s at baseline to 2 h postdose over the 12-week treatment period, full analysis population.

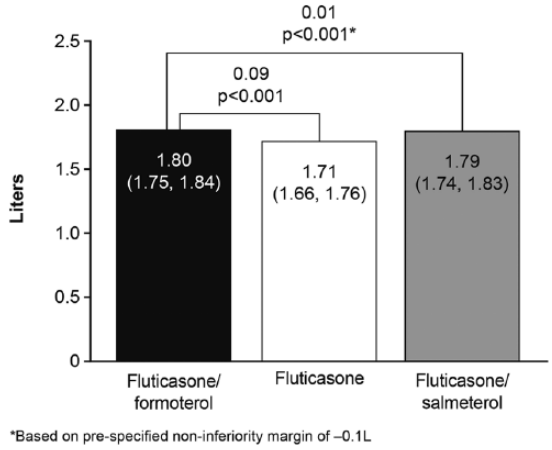

Figure 4. Forced expiratory volume in 1 s area under the curve over 4 h at week 12, full analysis population.

the difference was not statistically significant: LS mean treatment difference 0.03 l [95% CI: −0.01, 0.07 l, $p = 0.091$ (FAP)] (Figure 5). Given the Hochberg testing procedure employed, comparison of fluticasone/formoterol *versus* fluticasone/salmeterol was still undertaken in a confirmatory statistical manner, although statistical significance was to be declared at the 2.5% significance level, given the failure to demonstrate superiority of fluticasone/formoterol over fluticasone. Non-inferiority of fluticasone/formoterol compared with fluticasone/salmeterol was shown: LS mean treatment difference −0.02 l [95% CI: −0.06, 0.02 l, $p < 0.001$ (PPP)]. Again, very similar results were obtained for the alternate populations (PPP and FAP) for both treatment comparisons.

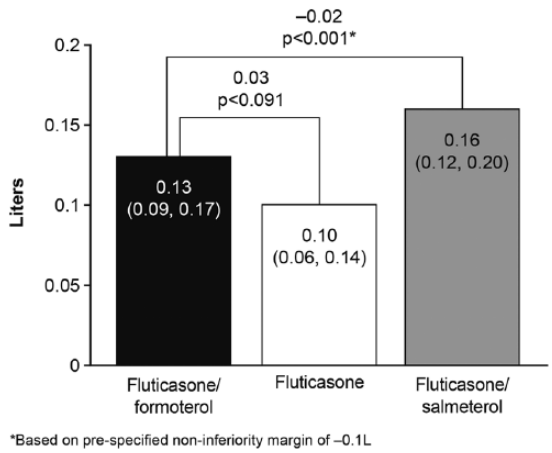

Figure 5. Change in predose forced expiratory volume in 1 s (litres) from baseline over the 12-week treatment period, full analysis population.

Other secondary endpoints

Lung function. FVC, FEF_{25}, FEF_{50}, FEF_{75} and $FEF_{25–75}$ were summarized descriptively. Other than FVC, all these endpoints exhibited numerically greater predose and 2 h postdose changes from baseline with fluticasone/formoterol and fluticasone/salmeterol than with fluticasone monotherapy, with generally similar treatment effects observed with the two combination therapies (Table 2).

Changes in clinic PEFR from predose at baseline to predose (Figure 6) and 2 h postdose (Figure 7) over the 12-week treatment period were greater with fluticasone/formoterol and fluticasone/salmeterol than with fluticasone monotherapy, whilst effects with the combination therapies were similar to one another.

Changes in daily (home) predose morning PEFR from baseline over the 12-week treatment period were greater with fluticasone/formoterol (16.49 l/min) than fluticasone (9.00 l/min): LS mean treatment difference 7.49 l/min [95% CI: 1.24, 13.75 l/min, $p = 0.019$ (FAP)]. Differences between fluticasone/salmeterol (12.67 l/min) and fluticasone, and between fluticasone/formoterol and fluticasone/salmeterol were nonsignificant at

Table 2. Change in forced vital capacity, forced expiratory flow at 25%, 50%, 75%, and between 25–75% at week 12: descriptive statistics, full analysis population.

		Predose, change from baseline*		2 h postdose, change from baseline*
	n	Mean (SD)	n	Mean (SD)
FVC (l)				
Fluticasone/formoterol	156	0.128 (0.2743)	146	0.195 (0.2417)
Fluticasone	149	0.151 (0.2625)	148	0.193 (0.2679)
Fluticasone/ salmeterol	156	0.170 (0.2344)	153	0.196 (0.2544)
FEF_{25} (l/s)				
Fluticasone/formoterol	156	0.570 (0.8283)	146	0.941 (0.8069)
Fluticasone	149	0.335 (0.6711)	148	0.408 (0.6099)
Fluticasone/ salmeterol	156	0.564 (0.7583)	153	0.891 (0.7790)
FEF_{50} (l/s)				
Fluticasone/formoterol	156	0.370 (0.6240)	146	0.714 (0.5995)
Fluticasone	149	0.176 (0.4986)	148	0.282 (0.5091)
Fluticasone/salmeterol	156	0.382 (0.5313)	153	0.652 (0.5683)
FEF_{75} (l/s)				
Fluticasone/formoterol	156	0.189 (0.3638)	146	0.343 (0.3832)
Fluticasone	149	0.077 (0.3780)	148	0.134 (0.3485)
Fluticasone/salmeterol	156	0.164 (0.4016)	153	0.338 (0.4284)
FEF_{25-75} (l/s)				
Fluticasone/formoterol	156	0.346 (0.5320)	146	0.622 (0.5180)
Fluticasone	149	0.139 (0.4583)	148	0.243 (0.4461)
Fluticasone/salmeterol	156	0.325 (0.5025)	153	0.578 (0.5248)

*Change from predose measurement at the baseline visit.
FEF, forced expiratory flow; FEF_{25}, forced expiratory flow at 25%; FVC, forced vital capacity; SD, standard deviation.

the 5% level. Results for the change from baseline in daily predose evening PEFR over 12 weeks were similar: fluticasone/formoterol *versus* fluticasone LS mean difference 6.54 l/min [95% CI: 0.37, 12.71 l/min, $p = 0.038$ (FAP)]. Again, differences between fluticasone/salmeterol and fluticasone, and between the combination treatments were nonsignificant at the 5% level (Table S2).

Symptoms. Substantial improvements in asthma symptom scores, the percentage of symptom-free days, sleep disturbance scores, the percentage of awakening-free nights, and the percentage of asthma control days were seen over the 12-week treatment period in all three treatment groups, with no between-group differences noted (Table 3).

During the treatment period, a high proportion of patients (approximately 57%) across all treatment groups fulfilled the protocol definition of a mild/moderate asthma exacerbation, that is, at least 2 consecutive days with: asthma-related sleep

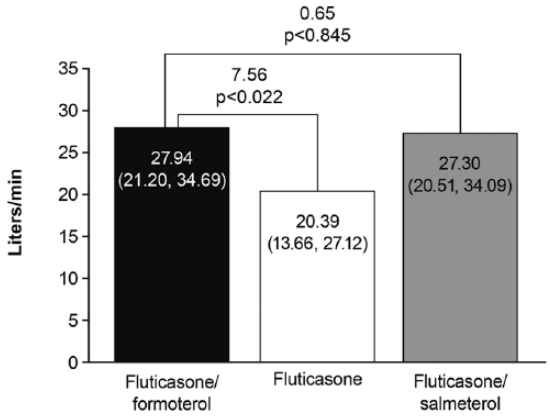

Figure 6. Change from clinic predose peak flow (PEFR) at baseline to predose PEFR over the 12-week treatment period, full analysis population.

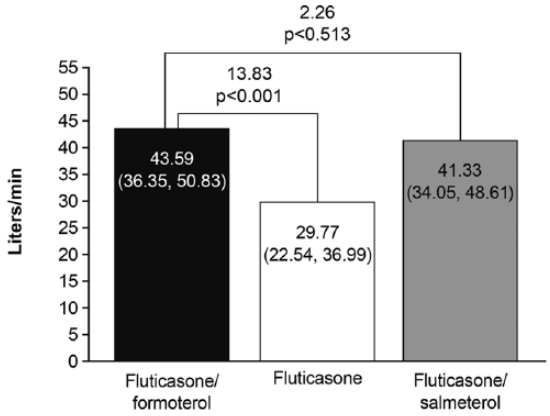

Figure 7. Change from clinic predose peak flow (PEFR) at baseline to 2 h postdose PEFR over 12-week treatment period, full analysis population.

disturbance, and/or ⩾4 puffs of rescue medication use, and/or >30% reduction in PEFR from baseline. It was observed that 59% of all mild/moderate exacerbation events qualified as such on the basis of sleep disturbance alone, that is, these events were not associated with either a concomitant deterioration in PEFR or with any use of rescue medication. This suggested that when many children awoke during the night for reasons other than asthma, these awakenings were wrongly recorded as being asthma-related awakenings in the patient diaries. A *post hoc* analysis of mild/moderate exacerbations was therefore undertaken in which the awakening criterion was omitted from the event definition. Per this definition, the event incidence was: fluticasone/formoterol 33.5%; fluticasone 28.1%; fluticasone/salmeterol 30.4%. There were no significant differences between treatment groups: fluticasone/formoterol *versus* fluticasone (odds ratio: 1.30; 95% CI: 0.81, 2.09), fluticasone/formoterol *versus* fluticasone/salmeterol (odds ratio: 1.20; 95% CI: 0.75, 1.92). The annualized rate of asthma exacerbations was 3.62 in the fluticasone/formoterol group, 3.91 in the fluticasone group (fluticasone/formoterol *versus* fluticasone rate ratio 0.97; 95% CI: 0.59, 1.58; $p = 0.900$), and 3.30 in the fluticasone/salmeterol group (fluticasone/formoterol *versus* fluticasone/salmeterol rate ratio 1.09; 95% CI: 0.66, 1.78; $p = 0.738$).

Four patients [none administered fluticasone/formoterol; two fluticasone (1.2%); two fluticasone/salmeterol (1.2%)] experienced a severe exacerbation during the treatment period, one of whom was hospitalized for asthma (in the fluticasone/salmeterol treatment group).

Similar improvements in PAQLQ score were observed in all treatment groups from a mean baseline of approximately 5.5 units to a mean of approximately 6.3 units, corresponding to 'hardly any' impairment of health status by week 12. Approximately 61% of patients across all treatment groups attained a clinically relevant improvement in health status (Table S3).

Mean ACQ scores at baseline were high (approximately 1.9 units) in all treatment groups, and in all groups decreased (improved) by approximately 1.0 unit by week 12, with no significant between-group differences. Approximately 75% of patients across treatment groups attained a clinically relevant reduction in ACQ score by week 12 (Table S4).

Safety. Overall, 125 (24.6%) patients experienced 203 on-treatment AEs. AEs were reported by slightly more patients in the fluticasone group [52 patients (30.2%)] than the fluticasone/formoterol group [38 patients (22.6%)] or the fluticasone/salmeterol group [35 patients (20.7%)]. The most commonly reported AEs are listed below in Table 4.

Most patients who reported AEs experienced mild events (80 patients, 15.7%) with only three patients experiencing a severe AE [bronchitis (fluticasone/formoterol), laryngitis (fluticasone) and upper limb fracture (fluticasone)]. The severe

Table 3. Asthma symptoms, full analysis population.

	Baseline		End of study		Change from baseline	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Asthma symptom scores						
Fluticasone/formoterol	167	0.90 (0.498)	164	0.21 (0.395)	164	−0.69 (0.564)
Fluticasone	170	0.89 (0.577)	168	0.22 (0.499)	167	−0.68 (0.717)
Fluticasone/salmeterol	167	0.88 (0.517)	165	0.21 (0.470)	164	−0.67 (0.608)
Percentage of symptom-free days						
Fluticasone/formoterol	167	29.26 (25.700)	164	73.03 (33.419)	164	43.76 (36.673)
Fluticasone	170	31.01 (29.562)	168	76.78 (31.410)	168	45.65 (39.370)
Fluticasone/salmeterol	167	29.69 (27.422)	165	75.32 (33.328)	165	45.71 (39.816)
Sleep disturbance scores						
Fluticasone/formoterol	167	0.66 (0.445)	164	0.14 (0.327)	164	−0.52 (0.458)
Fluticasone	170	0.69 (0.493)	167	0.14 (0.396)	166	−0.56 (0.632)
Fluticasone/salmeterol	167	0.67 (0.512)	165	0.08 (0.234)	164	−0.60 (0.512)
Percentage of awakening-free nights						
Fluticasone/formoterol	167	40.55 (30.327)	164	76.17 (29.264)	164	35.14 (34.703)
Fluticasone	170	37.65 (30.981)	167	77.58 (27.718)	167	39.77 (38.020)
Fluticasone/salmeterol	167	40.55 (34.142)	165	79.82 (24.385)	165	39.90 (38.492)
Asthma control days						
Fluticasone/formoterol	167	11.21 (15.932)	164	52.87 (36.360)	164	41.45 (36.874)
Fluticasone	170	10.93 (16.250)	167	55.68 (35.007)	167	44.64 (34.533)
Fluticasone/salmeterol	167	11.13 (18.583)	165	58.52 (36.148)	165	47.26 (37.844)

SD, standard deviation.

AEs of bronchitis and upper limb fracture were both classified as serious AEs (that is, requiring hospitalization), whilst the severe laryngitis led to discontinuation from the study. None of these were considered related to study medication by the investigator. Overall analyses of AEs, laboratory parameters and vital signs did not reveal any safety concerns or notable differences in the safety of profile of the three study treatments.

Discussion

The primary endpoint (2 h postdose FEV_1 over 12 weeks) and first key secondary endpoint (FEV_1 $AUC_{0–4}$ at week 12) reflect both ICS and LABA treatment effects.[20] Fluticasone/formoterol was shown to be superior to fluticasone and non-inferior to fluticasone/salmeterol for both of these endpoints.

A 4 h serial spirometry was employed in this study on the basis of earlier fluticasone/formoterol studies in which FEV_1 $AUC_{0–4\,h}$ and FEV_1 $AUC_{0–12\,h}$ were shown to be highly correlated (Pearson correlation coefficient, $R > 0.9$). The 4 h endpoint compared with 12 h serial spirometry is also advantageous because it means an inpatient stay for 4 h rather than 12, which is far more

Table 4. Most frequent adverse events, incidence (⩾2%) in any treatment group, safety population.

Preferred term	Fluticasone/formoterol	Fluticasone	Fluticasone/salmeterol
	(*n* = 168)	(*n* = 172)	(*n* = 169)
	n (%)	*n* (%)	*n* (%)
Patients with at least one AE	38 (22.6)	52 (30.2)	35 (20.7)
Bronchitis	3 (1.8)	2 (1.2)	4 (2.4)
Cough	2 (1.2)	4 (2.3)	2 (1.2)
Nasopharyngitis	4 (2.4)	15 (8.7)	13 (7.7)
Pharyngitis	4 (2.4)	7 (4.1)	4 (2.4)
Rhinitis	8 (4.8)	4 (2.3)	4 (2.4)
Viral rhinitis	1 (0.6)	2 (1.2)	4 (2.4)

AE, adverse event.

acceptable to pediatric patients and their carers. Additionally, approximately half the number of forced expiratory manoeuvres are required to define a 4 *versus* 12 h profile, thereby reducing the potential for fatigue and noncompliance to confound the resultant data. Prior to study commencement, the use of the 4 h endpoint was discussed and agreed with the European Medicines Agency's Pediatric Committee.

The third endpoint in the testing hierarchy was predose FEV_1 over 12 weeks, which measures ICS effect[20] when LABA effects are at their lowest ebb over the dosing interval. Superiority of fluticasone/formoterol over fluticasone was not confirmed for this endpoint. However, for all closely analogous endpoints in the study (predose morning diary FEV_1 over 12 weeks; predose clinic PEFR over 12 weeks; predose morning diary PEFR over 12 weeks) significant differences between fluticasone/formoterol and fluticasone were noted. Whilst non-inferiority between fluticasone/formoterol and fluticasone/salmeterol was confirmed for predose FEV_1 over 12 weeks, per the prespecified non-inferiority margin of −0.1 l and Hochberg testing procedure, it should be acknowledged that this endpoint possessed limited assay sensitivity given the modest observed difference between fluticasone/formoterol and fluticasone. This limitation was indeed the reason for the *a priori* designation of the predose FEV_1 endpoint in the third tier of the confirmatory testing hierarchy.

Results for multiple other secondary lung function endpoints supported the results for the primary efficacy endpoint; lung function effects with fluticasone/formoterol and fluticasone/salmeterol were in almost all cases similar to one another and numerically greater than those observed with fluticasone, whether predose or postdose.

By contrast, results for the symptom-related and exacerbation endpoints were very similar across all three treatment arms. Changes from baseline for symptomatic indices were large. For the ACQ and PAQLQ, mean treatment changes from baseline considerably exceeded the threshold for the minimum clinically relevant within-individual change.

Unlike for adults, in whom the additional symptomatic benefits of ICS/LABAs are clear, this study showed differences between ICS/LABA compared with ICS alone for lung function but not for symptom-based outcomes. This is well described in the literature: the majority of pediatric studies of ICS/LABAs have reported a similar pattern.[2,25–28] The reason for the apparent difference in adult and pediatric populations may be the difficulties in obtaining a subjective assessment from young children, who do not possess a clear perception of time and whose recall of events is frequently not reliable.[29] Thus, events occurring shortly before clinical examination may be those most prominent to younger children.[30] In addition, younger children are less able to

adequately verbalize their experiences,[30] whilst the perceived stigma associated with illness and a reluctance to differ from their healthy peers may result in under-reporting of symptoms.[29] Additionally, children subconsciously adapt their lifestyles to limit their symptom experience.[31] These factors may explain why reports of symptoms and activity limitation appear to be non-normally distributed in asthmatic children (i.e. skewed towards being 'healthy/normal')[32] and differ from the symptomatic impairment reported by adults with the same objective degree of lung function impairment.[29] Such issues may also explain why parents underestimate the severity of their children's symptoms: Kuehni and Frey reported that almost 40% of parents reported their child's asthma control to be 'excellent' when in fact it was 'poor' per asthma guideline control criteria.[31] Such factors may similarly explain why symptomatic benefits are generally not seen in children with other GINA Step 3 options, that is, medium-dose ICS[32–35] or ICS/leukotriene combinations,[36] when compared with low dose ICS.

It is less clear why, unlike in adults, ICS/LABAs do not appear to provide additional protection against severe exacerbations in children compared with ICS. It may be that severe events are also subject to the symptom-reporting issues described above, despite these events requiring therapeutic intervention, since the carer and physician must judge whether the child warrants review and then treatment. An alternative hypothesis is that stabilization of airway tone, a proposed mechanism by which LABAs reduce exacerbation risk,[37] may be relatively less important in children than in adults.

Results from the present study are nonetheless reassuring in that they provide no support for the view, based on earlier reports, that ICS/LABAs may be associated with an increased risk of severe exacerbations in children compared with ICS monotherapy.[38] Note that the majority of studies intimating the latter possibility did not assure coadministration of both drugs *via* a combination inhaler. Results from the recent US Food and Drug Administration mandated study by Stempel and colleagues also provide definitive evidence[39] in this regard: over 6000 children aged 4–11 years were randomized to single inhaler ICS/LABA (fluticasone/salmeterol) *versus* ICS (fluticasone at the same dose). There was no difference in the occurrence of serious asthma-related events (hospitalization, intubation, or death) between treatments. Additionally, there was no difference in the occurrence of exacerbations requiring systemic steroids, although a trend in favour of ICS/LABA was evident [hazard ratio 0.86 (95% CI: 0.73 to 1.01)]. The data from Stempel and colleagues therefore support the view that any potentially deleterious effect of LABA monotherapy upon airway inflammation is mitigated by the coadministration of an ICS.[40]

In addition to the severe exacerbation data from the present 12-week study (no events in the fluticasone/formoterol group and two in each of the other arms), further reassurance is available from an earlier open-label, pediatric study of fluticasone/formoterol:[15] of the 208 asthmatic children treated with fluticasone/formoterol over 36 weeks, none experienced an exacerbation requiring systemic corticosteroids or hospitalization.

Our study did not assess growth, nor did it include a higher dose ICS monotherapy comparator. However, in view of current GINA guidelines advocating medium doses of ICS as the preferred GINA Step 3 therapy, the results of the CAMP study and two recent meta-analyses are relevant. In CAMP, an ICS dose-dependent reduction in final adult height of 0.1 cm/μg/kg body weight was seen ($p = 0.007$).[41] Similar findings were reported by Loke and colleagues[42] and Pruteanu and colleagues[43] in their respective meta-analyses. Although these growth impairment effects are relatively modest, they vary across children and warrant consideration when escalating ICS doses in pediatric patients.

Finally, the BADGER study offers perhaps the most useful recent insight into treatment escalation in pediatric asthma and the potential limitations of parallel-group designs in settings where individual patient responses vary considerably. In this double-blind, three-way crossover study, children uncontrolled on low-dose ICS were treated with three different step-up options [medium-dose ICS, add-on LABA, and add-on leukotriene receptor antagonist (LTRA)] in separate, 16-week study periods.[44] For all pairwise treatment comparisons, a substantial proportion of patients responded better to the 'less successful' treatment. Thus, whilst a greater proportion of patients responded better to LABA add-on (54%) than to ICS dose escalation ($p = 0.002$), a large minority of 32% responded better to the

latter. A very similar result was seen for the LABA *versus* LTRA comparison. The study model employed by Lemanske and coworkers thus illustrates the diversity of step-up responses in children, which may further contribute to the difficulty evidencing symptomatic treatment differences in this population. Similarly designed studies may represent a more informative model with which to evaluate asthma treatments in future pediatric studies.

Conclusion

Fluticasone/formoterol was superior to fluticasone and non-inferior to fluticasone/salmeterol in terms of effects upon lung function. All three treatments elicited large improvements in symptomatic indices, but no differences between treatments were evident for these outcomes, as in earlier ICS/LABA studies. Few severe exacerbations were seen in this 12-week study, with none observed on fluticasone/formoterol. Safety profiles were similar for all three study treatments. Overall, these results support the efficacy and safety of fluticasone/formoterol in children.

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Conflict of interest statement

Kay Spooner is an employee of the study sponsor, Mundipharma Research Limited. Tammy McIver and Sanjeeva Dissanayake were employees of the study sponsor at the time this study was conducted.

Anna Ploszczuk and Miroslava Bosheva have no conflicts of interest to disclose.

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Etická komise FN Brno, Jihlavská 20, 625 00 Brno	Komisja Bioetyczna przy Dolnośląskiej Izbie Lekarskiej, ul. Matejki 6, 50-333 Wrocław
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Table S2 Change in Morning and Evening FEV_1 (Litres) and Peak Flow Measurements (Litres/Minute) from Baseline over the 12 Week Treatment Period, Full Analysis Population

Analysis Visit		Fluticasone/formoterol (N=167)	Fluticasone (N=171)	Fluticasone/salmeterol (N=168)
Change in diary morning FEV_1 from Baseline				
Overall	n	163	165	162
	LS Mean* (95% CI)	0.06 (0.02, 0.10)	0.01 (-0.03, 0.05)	0.02 (-0.02, 0.06)
	Difference† (95% CI of Difference)		0.06 (0.00, 0.11)	0.05 (-0.01, 0.10)
	P-Value‡		0.036	0.086
Change in diary evening FEV_1 from Baseline				
Overall	n	163	169	164
	LS Mean* (95% CI)	0.05 (0.01, 0.08)	0.01 (-0.02, 0.05)	-0.00 (-0.04, 0.03)
	Difference† (95% CI of Difference)		0.03 (-0.02, 0.08)	0.05 (-0.00, 0.10)
	P-Value‡		0.203	0.060
Change in Morning Peak Flow Measurements				
Overall	n	167	169	166
	LS Mean* (95% CI)	16.49 (11.50, 21.48)	9.00 (4.03, 13.97)	12.67 (7.68, 17.67)
	Difference† (95% CI of Difference)		7.49 (1.24, 13.75)	3.82 (-2.48, 10.12)
	P-Value‡		0.019	0.234
Change in Evening Peak Flow Measurements				
Overall	n	167	170	166
	LS Mean* (95% CI)	14.22 (9.53, 18.91)	7.68 (3.03, 12.34)	11.92 (7.19, 16.64)
	Difference† (95% CI of Difference)		6.54 (0.37, 12.71)	2.31 (-3.91, 8.52)
	P-Value‡		0.038	0.466
Change in Peak Flow from pre-dose baseline to pre-dose at Week 12				
Overall	n	166	167	165
	LS Mean* (95% CI)	27.94 (21.20, 34.69)	20.39 (13.66, 27.12)	27.30 (20.51, 34.09)
	Difference† (95% CI of Difference)		7.56 (1.07, 14.04)	0.65 (-5.87, 7.17)
	P-Value‡		0.022	0.845
Change in Peak Flow Measurements from pre-dose baseline to 2-hours post-dose at Week 12				
Overall	n	165	165	165
	LS Mean* (95% CI)	43.59 (36.35, 50.83)	29.77 (22.54, 36.99)	41.33 (34.05, 48.61)
	Difference† (95% CI of Difference)		13.83 (7.06, 20.59)	2.26 (-4.53, 9.05)
	P-Value‡		<0.001	0.513

N: Number of patients in population. n: Number of patients with data available. CI: Confidence Interval. FEV1: forced expiratory volume in the 1st second.
Note: Daily morning peak flow measurement was calculated from the patient's diary for the 7 days prior to the visit.
*Least square mean from a repeated measures ANCOVA with fixed terms for treatment, age group, PEFR at baseline, visit and treatment by visit interaction, and centre as a random effect. † Difference: LS Mean Flutiform - LS Mean Fluticasone/Seretide. ‡P-value of the pairwise treatment comparisons (based on the null hypothesis that there is no difference in treatment means).

Table S3 Change in PAQLQ Overall Score from Baseline to Week 12 of >= 0.5 Units, Stratified by Age Group, Full Analysis Population

	Fluticasone/formoterol	Fluticasone	Fluticasone/salmeterol
Age Group = 5 to 6 years			
N	27	31	24
Yes*	17 (63.0)	20 (64.5)	15 (62.5)
No	7 (25.9)	8 (25.8)	7 (29.2)
Missing	3 (11.1)	3 (9.7)	2 (8.3)
Odds Ratio**		1.51	3.16
95% CI**		(0.24, 9.75)	(0.40, 24.66)
Age Group = 7 to <12 years			
N	140	140	144
Yes*	83 (59.3)	84 (60.0)	89 (61.8)
No	51 (36.4)	43 (30.7)	46 (31.9)
Missing	6 (4.3)	13 (9.3)	9 (6.3)
Odds Ratio**		0.98	0.87
95% CI**		(0.52, 1.82)	(0.47, 1.59)
Overall			
N	167	171	168
Yes*	100 (59.9)	104 (60.8)	104 (61.9)
No	58 (34.7)	51 (29.8)	53 (31.5)
Missing	9 (5.4)	16 (9.4)	11 (6.5)
Odds Ratio**		1.02	0.96
95% CI**		(0.57, 1.84)	(0.54, 1.71)

PAQLQ-IA: Paediatric Asthma Quality of Life Questionnaire - Interviewer Administered. N: Number of patients in population. n: Number of patients with data available. %: Percentage based on N. CI: Confidence Interval.
* Patients with a change in PAQLQ overall score from baseline to week 12 of >= 0.5 units.
** Logistic regression estimates with fixed terms for treatment, age (years) and PAQLQ score at baseline, and centre as a random effect.

Table S4 Reduction in ACQ-IA Overall Score from Baseline to Week 12 of >= 0.5 Units, Stratified by Age Group, Full Analysis Population

	Fluticasone/formoterol (N=167)	Fluticasone (N=171)	Fluticasone/salmeterol (N=168)
Age group = 5			
N	12	11	6
Yes*	10 (83.3)	7 (63.6)	5 (83.3)
No	2 (16.7)	2 (18.2)	-
Missing	-	2 (18.2)	1 (16.7)
Odds Ratio**		NC	NC
95% CI**		NC	NC
Age group = 6 – 10 years			
N	126	129	126
Yes*	92 (73.0)	102 (79.1)	98 (77.8)
No	26 (20.6)	17 (13.2)	21 (16.7)
Missing	8 (6.3)	10 (7.8)	7 (5.6)
Odds Ratio**		0.75	0.85
95% CI**		(0.36, 1.56)	(0.42, 1.72)
Age group = 11 years			
N	29	31	36
Yes*	20 (69.0)	21 (67.7)	24 (66.7)
No	7 (24.1)	7 (22.6)	7 (19.4)
Missing	2 (6.9)	3 (9.7)	5 (13.9)
Odds Ratio**		0.75	0.59
95% CI**		(0.19, 2.93)	(0.15, 2.26)
Overall			
Yes*	122 (73.1)	130 (76.0)	127 (75.6)
No	35 (21.0)	26 (15.2)	28 (16.7)
Missing	10 (6.0)	15 (8.8)	13 (7.7)
Odds Ratio**		0.79	0.81
95% CI**		(0.42, 1.48)	(0.44, 1.50)

ACQ-IA: Asthma Control Questionnaire - Interviewer administered. N: Number of patients in population. n: Number of patients with data available. %: Percentage based on N. CI: Confidence Interval.
NC = Not calculable.
* Patients with a reduction in ACQ-IA overall score from baseline to week 12 of >= 0.5 units.
** Logistic regression estimates with fixed terms for treatment, age (years) and ACQ-IA score at baseline, and centre as a random effect.