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Efficacy and safety of fluticasone/formoterol combination therapy in patients with moderate-to-severe asthma

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Summary
Background: The inhaled corticosteroid, fluticasone propionate, and the long-acting β_2-adrenergic agonist, formoterol fumarate, are both highly effective treatments for bronchial asthma. This study (NCT00393952/EudraCT number: 2006-005989-39) compared the efficacy and safety of fluticasone/formoterol combination therapy (***flutiform***®; 250/10 μg) administered twice daily (b.i.d.) via a single aerosol inhaler, with the individual components (fluticasone 250 μg b.i.d.; formoterol 10 μg b.i.d.), in adult and adolescent patients with moderate-to-severe asthma.
Methods: This was a 12-week, double-blind, randomised, parallel-group, multicentre, placebocontrolled phase 3 study. The co-primary efficacy endpoints were: i) the mean change in the forced expiratory volume in the first second (FEV_1) from morning pre-dose at baseline to pre-dose at week 12 (fluticasone/formoterol 250/10 μg vs. formoterol), ii) the mean change in FEV_1 from morning pre-dose at baseline to 2 h post-dose at week 12 (fluticasone/formoterol 250/10 μg vs. fluticasone), and iii) the number of patients who discontinued prematurely due to lack of treatment efficacy (fluticasone/formoterol 250/10 μg vs. placebo). The secondary endpoints included measures of lung function, disease control, and asthma symptoms. Safety was assessed based on adverse events, vital signs, and clinical laboratory evaluations.
Results: Overall, 395 (70.9%) patients completed the study. Fluticasone/formoterol 250/10 μg b.i.d. was superior to the individual components and placebo for all three co-primary

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endpoints and demonstrated numerically greater improvements for multiple secondary efficacy analyses. Fluticasone/formoterol combination therapy had a good safety profile over the 12 weeks.
Conclusion: Fluticasone/formoterol combination therapy will provide clinicians with an efficacious alternative treatment option for patients with moderate-to-severe asthma.

Introduction

Asthma is a chronic inflammatory airway disorder, associated with variable airflow limitation as a result of exaggerated bronchoconstriction, airway hyperresponsiveness and mucus hypersecretion.[1,2] It is estimated to affect at least 300 million people and represents approximately 1% of the total disease burden worldwide.[1,3,4]

Inhaled corticosteroids (ICSs) are the first line of therapy in targeting airway inflammation and hyperresponsiveness and are the mainstay of therapy for asthma of all severity levels.[1,5–7] In patients who present with moderate, persistent asthma, or who have uncontrolled symptoms despite the use of a low to moderate dose of ICS, current guidelines recommend the addition of an inhaled long-acting β_2-adrenergic agonist (LABA) which alleviates asthma symptoms for at least 12 h[1,8] The addition of a LABA to ICS therapy has been shown to be clinically more effective than doubling the dose of ICS administered, with greater improvements in lung function, and reductions in exacerbations and days with poorly controlled asthma.[1,6,8–12] The benefits of ICS/LABA therapy are supported by *in vitro* research suggesting that, at the molecular level, the two compounds exert a synergistic mechanism of action when suppressing airway inflammation and alleviating bronchoconstriction, respectively.[13–16]

This has led to the development of ICS/LABA single inhaler combination therapy.[17–22] The likelihood of patient adherence to a treatment regimen is increased with the use of asthma therapy administered via a single inhaler, which may, as a consequence, lead to improved asthma control in terms of better lung function and a reduction in asthma exacerbations.[23,24] However, despite the commercial availability of efficacious combination therapies, asthma remains poorly controlled for a significant proportion of patients.[4,25–28]

Fluticasone propionate (fluticasone) is a potent ICS with a well-established efficacy and safety profile,[18,29–33] while formoterol fumarate (formoterol) is a LABA with a rapid onset of action of between 1 and 3 min, and sustained, dose-dependent bronchodilatory effects.[32–36]

The present study was undertaken to evaluate the efficacy and tolerability of a new asthma therapy combining fluticasone and formoterol, administered twice daily (b.i.d.) via a single aerosol inhaler (fluticasone/formoterol 250/10 μg), in adult and adolescent patients with moderate-to-severe asthma.

Methods

This was a 12-week, randomised, double-blind, placebo- and active-controlled, stratified, parallel-group study, performed at 78 centres in North America and Europe (July 2006 to April 2008; EudraCT number: 2006-005989-39; US NCT number: NCT00393952). The study was conducted in accordance with the International Conference on Harmonisation guidelines on Good Clinical Practice and the ethical principles of the Declaration of Helsinki. The protocol was reviewed and approved by the Institutional Review Boards or Independent Ethics Committees of the respective participating centres and all patients, or the parents or guardians of those less than 18 years of age, provided written informed consent before enrolment.

Patients

Male and female patients, aged 12 years and over, with a history of symptomatic asthma for at least 12 months prior to screening, as defined by the National Asthma Education and Prevention Program,[37] were eligible for inclusion in this study. Eligible patients had a documented use of ICS therapy for at least 4 weeks prior to screening at a dose of no more than 500 μg/day inhaled fluticasone (or equivalent ICS dose). At both screening and baseline (week 0), all patients were required to have a forced expiratory volume in the first second (FEV_1) between 40% and 80% (inclusive) of predicted normal values following appropriate withholding of bronchodilator medication; treatment with any LABA therapy was discontinued at least 24 h, and with any short-acting β_2-agonist at least 6 h, prior to the first pulmonary function test. Patients were also required to demonstrate FEV_1 reversibility ($\geq$14.5% increase in FEV_1 15—30 min following albuterol/salbutamol aerosol inhalation) within 12 months prior to or at the screening visit. During any 7 consecutive days of the 14 $\pm$ 3 day run-in period, patients had to use 2 or more inhalations per day of rescue medication (albuterol/salbutamol) for at least 3 days and to either have at least 3 days with asthma symptoms or one night with sleep disturbance due to asthma in order to be eligible for randomisation. All patients were required to demonstrate satisfactory aerosol technique and correct use of the telephone diary system.

Patients were excluded from the study if they had a history of life-threatening asthma, hospitalisation or prior intubation for asthma either during the previous 12 months or during the run-in period. If patients had used systemic corticosteroids within 3 months, omalizumab within 6 months or a leukotriene receptor antagonist within a week prior to screening, they were also excluded. If patients had significant, non-reversible pulmonary disease (e.g. chronic obstructive pulmonary disease, cystic fibrosis or bronchiectasis), or experienced respiratory tract infections within the 4 weeks prior to screening or during the run-in, a significant medical illness, had a smoking history of at least 10 pack-years or within the previous 12 months, or hypersensitivity to

any study medication, they were excluded from the study. Patients receiving β-blockers, tricyclic antidepressants, monoamine oxidase inhibitors, quinidine-type antiarrhythmics, or drugs known to inhibit CYP3A4, within the week prior to the screening visit were also ineligible for participation.

Treatments

During the open-label run-in period, patients received fluticasone as asthma maintenance therapy at a dose that was dependent on individual steroid usage prior to screening: patients who were taking less than 250 μg fluticasone (or equivalent ICS dose) per day received 100 μg/day fluticasone (1 actuation 50 μg fluticasone b.i.d.), and patients requiring more than 250 μg fluticasone (or equivalent ICS dose) per day received 200 μg/day fluticasone (2 actuations 50 μg fluticasone b.i.d.). All study participants were permitted the use of rescue albuterol/salbutamol, as needed, for worsening asthma symptoms.

At the end of the run-in period, patients who met the randomisation criteria, as described above, were assigned equally to one of the five, blinded treatment arms (Fig. 1). Every morning and evening throughout the 12-week study period, each patient self-administered two actuations from two aerosol devices, for a total of 8 inhalations per day, according to their allocated treatment arm: 2 actuations of 125/5 μg b.i.d. fluticasone/formoterol and placebo b.i.d. (both hydrofluoroalkane [HFA] pMDI, SkyePharma), 2 actuations of fluticasone 125 μg b.i.d. (*Flovent*® HFA pMDI, GlaxoSmithKline) and placebo b.i.d., 2 actuations of formoterol 5 μg b.i.d. (HFA pMDI, SkyePharma, Switzerland) and placebo b.i.d., 2 actuations of fluticasone/formoterol 50/5 μg b.i.d. and placebo b.i.d., or 2 actuations b.i.d. from two devices both containing placebo. With the exception of salbutamol/albuterol rescue medication, all other asthma medications were prohibited during the study. Study medications were administered via a pMDI without the use of a spacer. Patients received instructions and training on their use during the screening visit, and inhaler technique and dosing procedures were reviewed at each study visit. Patients were instructed to take morning and evening doses as evenly spaced as possible, and were required to leave a 1-min interval between inhalations and wash their mouth thoroughly after dosing.

Patients were randomised according to minimisation with biased coin assignment[38] and treatment groups were balanced on baseline FEV_1 % predicted (40%—60% or >60%—80%), study site, and the subgroup of patients aged 12—18 years. An Interactive Voice Response System was used for subject enrolment and treatment allocation, and blinding was maintained throughout the study with the use of dummy placebo inhalers. All investigators, personnel at the study site, and representatives involved in monitoring, data management and any other aspect of the trial, including sponsor personnel, were blinded throughout the study. Adherence to study medication was assessed based on the number of actuations of study and rescue medication recorded by patients throughout the run-in and treatment periods. The baseline visit was at week 0 and followed the run-in. Patients were scheduled to visit the sites for clinical assessments at weeks 2, 4, 8, and 12 (or final visit for early discontinuations), and a safety follow-up was carried out by telephone 2 weeks following the last dose of study medication.

Efficacy assessments

The primary objective of the study was to evaluate the efficacy of fluticasone/formoterol 250/10 μg b.i.d. combination therapy compared with fluticasone, formoterol, and placebo using three co-primary endpoints. The efficacy of the fluticasone component of fluticasone/formoterol 250/10 μg b.i.d. was evaluated by comparing the combination product with formoterol alone using the mean change in FEV_1 from pre-dose at baseline (week 0) to pre-dose at week 12. The efficacy of the formoterol component of fluticasone/formoterol 250/10 μg b.i.d. was assessed by comparing the combination product with fluticasone alone using the mean change in FEV_1 from pre-dose at baseline to 2 h post-dose at week 12. The efficacy of the combination product compared with placebo was demonstrated by the time to discontinuation due to lack of efficacy, defined as either a severe exacerbation or the loss of asthma control, with the two classifications combined for the analysis. A severe exacerbation was defined as the deterioration in the patient's asthma requiring additional therapy such as a systemic steroid, a visit to the emergency room or hospitalisation due to asthma. The loss of asthma control was defined as a decrease in pre-dose FEV_1 of more than 20%

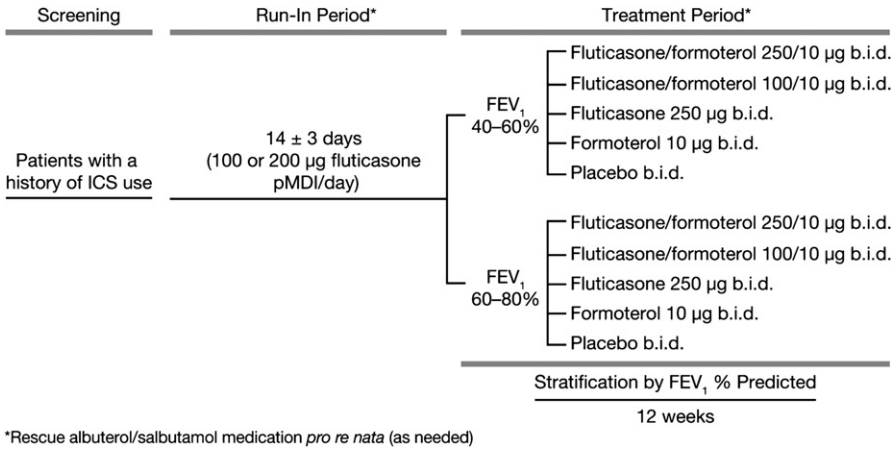


Figure 1 Study design.

from baseline; a decrease in morning pre-dose peak expiratory flow rate (PEFR) of more than 25% from baseline on more than 3 of the 7 days before a study visit; excessive use ($\geq$12 actuations per day) of rescue medication on more than 3 of the 7 days before a study visit, and nocturnal awakenings due to asthma that required rescue medication use on more than 2 of 7 days before a study visit.

Secondary efficacy endpoints included both data obtained from the telephone diaries and from additional pulmonary function tests. Patient recorded data included morning and evening PEFR; rescue medication use; asthma symptom scores (from 0 for no symptoms to 5 for where asthma was so severe that the patient was unable to go to work or school or carry out normal daily activities); symptom-free days (defined as days with asthma symptom score of 0); rescue medication-free days (defined as days with no use of rescue medication); asthma control days (defined as days with an asthma score of 0, a sleep disturbance score of 0, and no use of rescue medication); type and frequency of asthma exacerbations (defined as mild to moderate if the pre-dose morning PEFR measurement was more than 30% below baseline values, or if the patient experienced awakening at night due to asthma for at least 2 consecutive days, or if they had to use additional rescue medication of more than 3 inhalations/day compared with baseline on at least 2 consecutive days; or as severe exacerbations, as defined above); sleep disturbance scores (from 0 where patient slept through the night and experienced no asthma to 4 where the patient could not sleep at all due to asthma), and awakening-free nights (defined as nights with a sleep disturbance score of 0).

Additional pulmonary function tests included changes from baseline to each post-dose time point in FEV_1, PEFR, FEV_1 % predicted normal, and forced vital capacity (FVC). In addition, the 12-h serial FEV_1 area under the curve (AUC) was to be assessed in a subset population, whereby serial pulmonary function tests were also performed post-dose at 6, 8, 10, and 12 h following the morning dose at weeks 0, 2, and 12. The FEV_1 AUC analyses were carried out to determine the efficacy of the 250/10 μg combination product compared with each of the monocomponents and placebo.

FEV_1 was measured[39] at baseline and at weeks 2, 4, 8, and 12, and the predicted FEV_1 values from Polgar and Promadhat[40] and Crapo et al[41] were used for adolescents (12—17 years) and adults ($\geq$18 years), respectively. In addition to age, height, and sex, the predicted spirometry values were also adjusted for race.

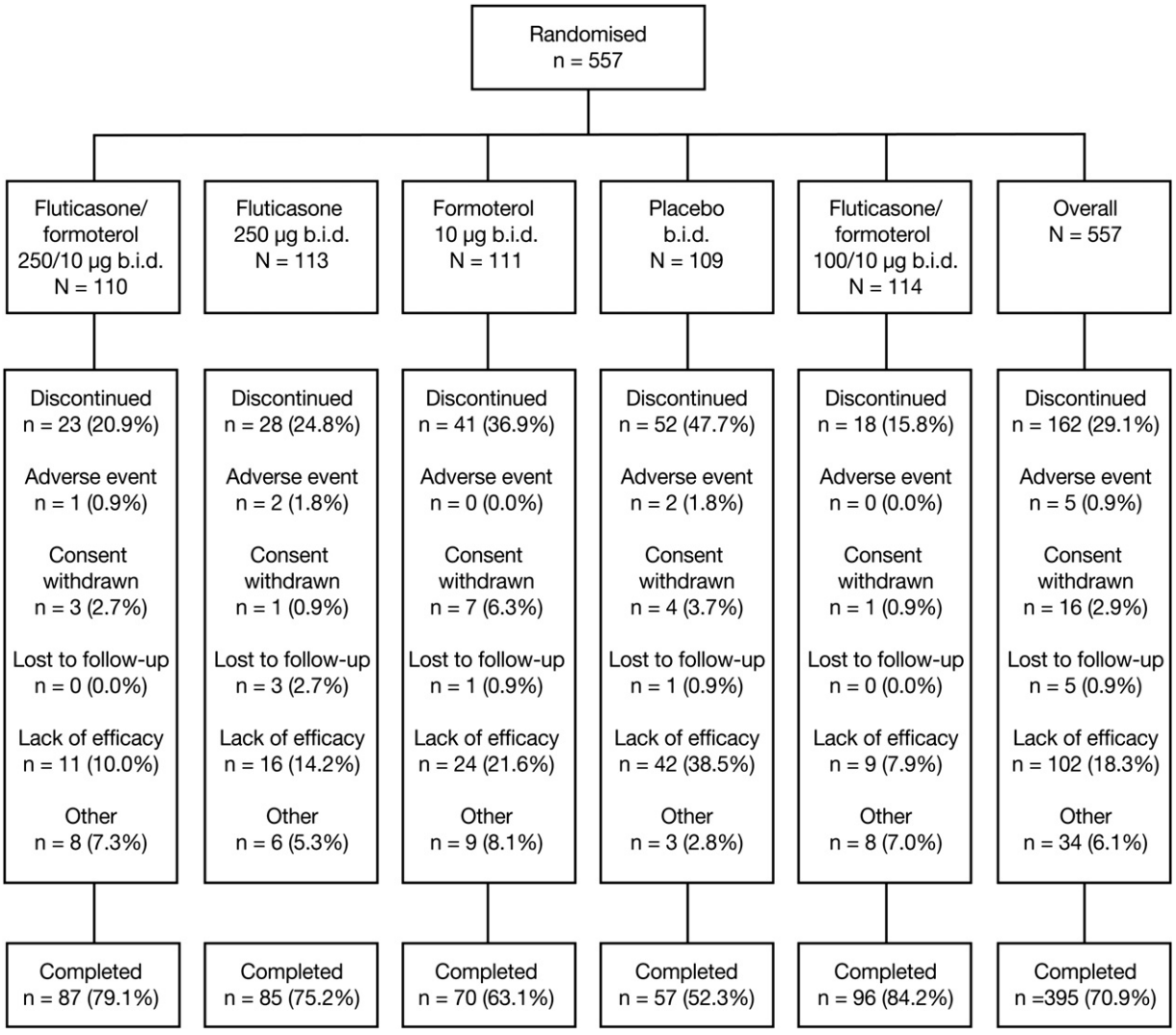


Figure 2 Patient flow diagram.

Table 1 Demographic and asthma characteristics, safety population.

Characteristic	Treatment group					
	Fluticasone/Formoterol 250/10 μg b.i.d N = 110	Fluticasone 250 μg b.i.d. N = 113	Formoterol 10 μg b.i.d. N = 111	Placebo b.i.d. N = 109	Fluticasone/Formoterol 100/10 μg b.i.d. N = 113	Overall N = 556
Gender, n (%)						
Female	64 (58.2)	63 (55.8)	67 (60.4)	71 (65.1)	67 (59.3)	332 (59.7)
Male	46 (41.8)	50 (44.2)	44 (39.6)	38 (34.9)	46 (40.7)	224 (40.3)
Ethnic origin, n (%)						
White/Caucasian	92 (83.6)	89 (78.8)	91 (82.0)	94 (86.2)	99 (87.6)	465 (83.6)
Black	13 (11.8)	12 (10.6)	13 (11.7)	8 (7.3)	6 (5.3)	52 (9.4)
Asian	0	0	0	1 (0.9)	1 (0.9)	2 (0.4)
Hispanic	5 (4.5)	10 (8.8)	7 (6.3)	5 (4.6)	6 (5.3)	33 (5.9)
Other	0	2 (1.8)	0	1 (0.9)	1 (0.9)	4 (0.7)
Age, years						
Mean (SD)	44.8 (15.66)	41.9 (15.17)	42.8 (15.51)	42.6 (15.48)	43.4 (14.22)	43.1 (15.19)
Median	46.5	44.0	45.0	43.0	45.0	45.0
Min–Max	12–80	12–76	12–82	12–79	12–72	12–82
Age categories, n (%)						
12–17 y	8 (7.3)	9 (8.0)	9 (8.1)	6 (5.5)	9 (8.0)	41 (7.4)
≥ 18 y	102 (92.7)	104 (92.0)	102 (91.9)	103 (94.5)	104 (92.0)	515 (92.6)
Baseline FEV_1 % predicted, *n* (%)						
40%–60%	36 (32.7)	37 (32.7)	37 (33.3)	36 (33.0)	37 (32.7)	183 (32.9)
>60%–80%	74 (67.3)	76 (67.3)	74 (66.7)	73 (67.0)	76 (67.3)	373 (67.1)
Duration of asthma[a], years						
Mean (SD)	20.25 (14.606)	19.93 (14.960)	19.08 (14.468)	21.12 (15.323)	21.72 (15.080)	20.42 (14.866)
Median	16.95	14.70	15.00	18.90	19.10	16.75
Min–Max	1.1–63.3	1.2–63.3	1.1–64.1	1.2–69.3	2.0–61.9	1.1–69.3
FEV_1 % predicted[b] at baseline[c]						
Mean (SD)	64.9 (10.45)	65.7 (18.36)	65.3 (11.36)	64.1 (10.78)	64.3 (11.58)	64.9 (12.85)
Median	66.0	67.0	67.0	65.0	65.0	66.0
Min–Max	41–89	39–225[d]	40–102	41–82	40–105	39–225
FEV_1at baseline[c], L						
Mean (SD)	2.082 (0.5512)	2.140 (0.5850)	2.136 (0.6246)	2.068 (0.5222)	2.098 (0.5871)	2.105 (0.5740)
Median	2.025	2.080	2.070	2.060	2.010	2.055
Min–Max	1.05–3.53	0.96–3.91	0.91–4.10	1.09–3.34	0.91–3.94	0.91–4.10
Reversibility at screening, %	N = 109	N = 113	N = 109	N = 111	N = 109	N = 551
Mean (SD)	24.67 (11.949)	27.95 (14.556)	26.98 (12.353)	26.99 (14.749)	25.72 (12.658)	26.46 (13.297)
Median	20.00	22.70	22.50	21.80	21.60	21.70
Min–Max	14.6–78.4	14.6–109.6	14.5–74.3	10.1–91.2	14.6–92.7	10.1–109.6

[a] Duration of asthma calculated as (date of screening visit from demographics CRF - asthma diagnosis date)/365.25 and rounded to 1 decimal place.
[b] Based on standardised predicted FEV_1 values.
[c] Baseline was the last available value prior to dosing at the baseline/week 0 visit.
[d] Patient was a 36-year-old Caucasian female who weighed 64 kg with a height of 104 cm.

Another secondary endpoint included the assessment of the treatment efficacy in terms of lung function, disease control, and asthma symptoms, for fluticasone/formoterol combination therapy at the 100/10 μg b.i.d. dose level.

Safety assessments

Safety was assessed throughout the study based on adverse events, vital signs, a 12-lead electrocardiogram (ECG), and clinical laboratory testing.

Statistical analyses and sample size calculation

Efficacy analyses were carried out on the full analysis set (FAS), which included all randomised patients who had at least one dose of study medication, a pre-dose FEV_1 measurement at baseline, a pre-dose FEV_1 measurement post-baseline, and a 2-h post-dose FEV_1 measurement post-baseline. The per-protocol (PP) population comprised all patients in the FAS who did not have a major protocol violation; the safety population included all patients who received at least one inhalation of study medication after randomisation, and the AUC population included all patients who participated in the subset of 12-h post-dose serial pulmonary function tests and who had a minimum of four measured FEV_1 values.

An analysis of covariance (ANCOVA) determined the change in FEV_1 from pre-dose at baseline (week 0) to pre-dose and to 2 h post-dose at week 12, with treatment group (fluticasone/formoterol 250/10 μg b.i.d., fluticasone, formoterol, and placebo), study centre, and baseline FEV_1 % predicted category (40%–60% or >60%–80%) as factors, and baseline FEV_1 as a continuous covariate. A stratified log-rank test was performed for the analysis of discontinuations due to lack of efficacy, adjusting for baseline FEV_1 % predicted category. Only the two relevant treatment groups being compared were included in the analyses.

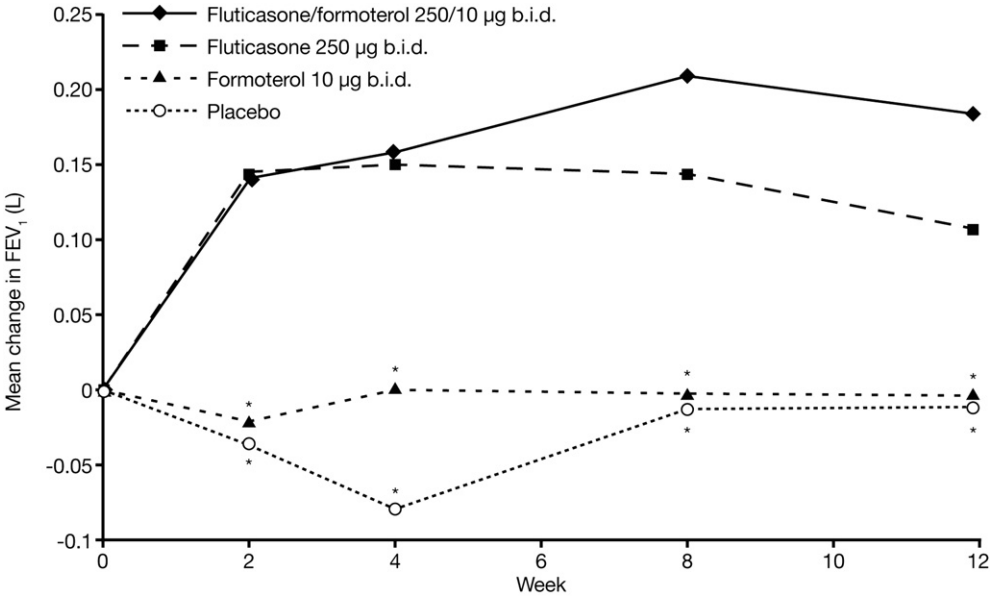
Statistical analyses of the following secondary efficacy endpoints were carried out using an ANCOVA as for the co-primary endpoints: the difference between fluticasone/formoterol 250/10 μg b.i.d. and the comparators (fluticasone, formoterol, and placebo) with respect to change from pre-dose at baseline to both pre-dose, and 2 h post-dose, at weeks 2, 4, 8, and 12 for FEV_1, PEFR, FEV_1 % predicted normal and FVC, with the relevant baseline value as the covariate; morning and evening PEFR; asthma symptom scores; sleep disturbance scores, and rescue medication use. Differences between treatment groups, for the change from baseline to week 12, for symptom-free days, rescue medication-free days, asthma control days, and awakening-free nights were assessed using van Elteren's method for combining Wilcoxon rank sum test results from independent strata, with baseline FEV_1 % predicted category and study site as the main effects. Differences between the treatment groups for the proportion of patients who reported at least one treatment-emergent asthma exacerbation were assessed using logistic regression with effects for the four treatment groups (fluticasone/formoterol 250/10 μg b.i.d., fluticasone, formoterol, and placebo), and baseline FEV_1 % predicted category.

If all three co-primary endpoints were statistically significant then the secondary endpoints were evaluated in a confirmatory manner using a sequential gatekeeper approach.[42] The order for the treatment comparisons was as follows: i) fluticasone/formoterol 250/10 μg b.i.d. combination product vs. placebo, and ii) fluticasone/formoterol 250/10 μg b.i.d. combination product vs. fluticasone alone and vs. formoterol alone. The first four secondary endpoints were analysed in the following order, based on the mean change from baseline to week 12: morning PEFR, evening PEFR, rescue medication use, and asthma symptom scores. The first comparative test was combination product vs. placebo for each of these four endpoints. If each of these tests returned statistically significant results (statistical analyses were

Table 2 Mean change in FEV_1 (L) from pre-dose at baseline to pre-dose and to 2 h post-dose at week 12 using last observation carried forward imputation, full analysis set.

	Treatment group			
	Fluticasone/Formoterol 250/10 μg b.i.d. N = 108	Fluticasone 250 μg b.i.d. N = 109	Formoterol 10 μg b.i.d. N = 110	Placebo b.i.d. N = 105
Baseline FEV_1 (L) Mean (SD)	2.085 (0.5509)	2.134 (0.5848)	2.143 (0.6237)	2.066 (0.5154)
Change in FEV_1 from pre-dose at baseline to pre-dose at week 12				
LS Mean (SE)[a]	0.184 (0.043)	0.106 (0.041)	−0.004 (0.041)	−0.011 (0.043)
Difference from fluticasone/formoterol 250/10 μg b.i.d.: contribution of fluticasone component				
LS Mean (SE)[a]		NA	0.189 (0.056)	NA
95% CI[a]		NA	0.079, 0.298	NA
p-value[a]		NA	< 0.001	NA
Change in FEV_1 from pre-dose at baseline to 2 h post-dose at week 12				
LS Mean (SE)[a]	0.357 (0.040)	0.211 (0.039)	0.292 (0.039)	0.123 (0.040)
Difference from fluticasone/formoterol 250/10 μg b.i.d.: contribution of formoterol component				
LS Mean (SE)[a]		0.146 (0.053)	NA	NA
95% CI[a]		0.042, 0.250	NA	NA
p-value[a]		0.006	NA	NA

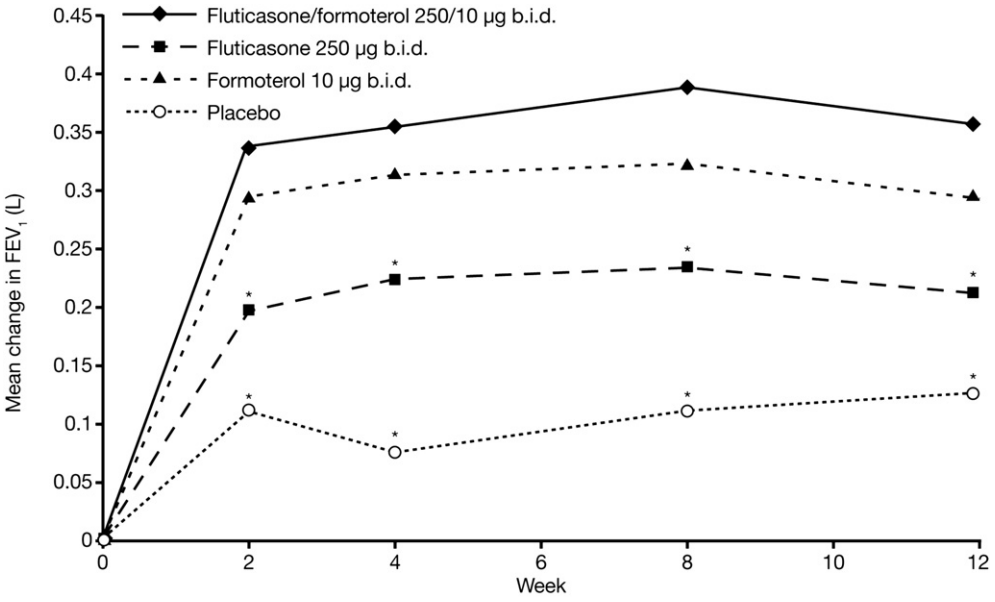
SD = standard deviation; LS = least squares; SE = standard error; NA = not applicable; CI = confidence interval; b.i.d. = twice daily.
[a] LS mean, SE, CI, and *p*-value are from ANCOVA with factors for displayed treatment groups (fluticasone/formoterol 250/10 μg b.i.d., fluticasone, formoterol, and placebo), site, and baseline FEV_1 % predicted category, with baseline FEV_1 value as a continuous covariate.



*p ≤0.05 versus fluticasone/formoterol 250/10 µg b.i.d. treatment group.
Baseline means were 2.085 L, 2.134 L, 2.143 L, and 2.066 L for the fluticasone/formoterol 250/10 µg b.i.d., fluticasone, formoterol, and placebo treatment groups, respectively, for all patients in the full analysis set.
b.i.d. = twice daily

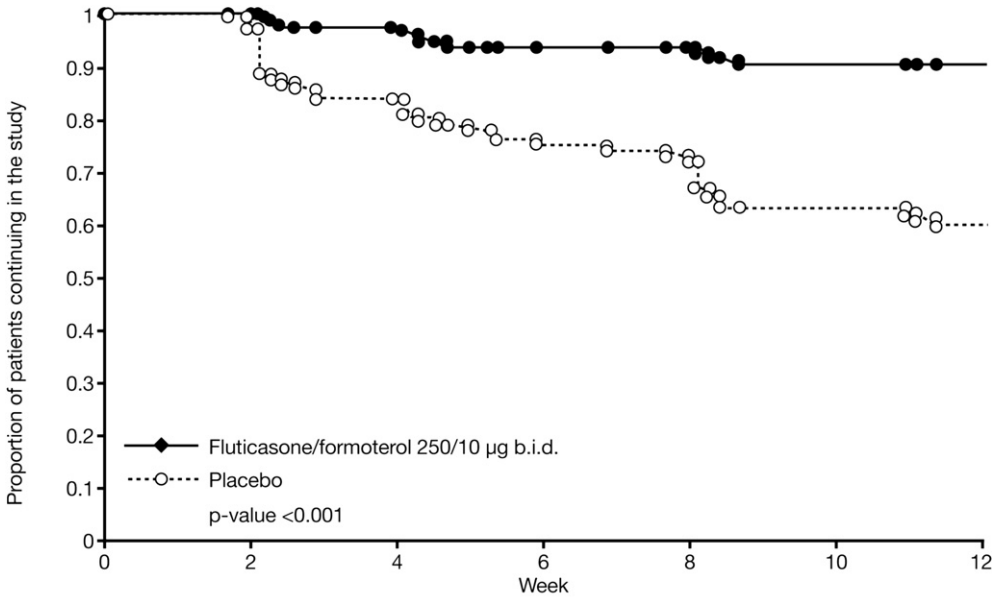
Figure 3 Mean change in FEV_1 (L) from pre-dose at baseline to pre-dose at weeks 2, 4, 8, and 12: the contribution from the fluticasone component of fluticasone component of fluticasone/formoterol 250/10 µg b.i.d. combination therapy, full analysis set using last observation carried forward imputation.

two-sided and significance was measured at the 0.05α level), then comparative testing could be carried out for combination therapy vs. fluticasone and vs. formoterol for each of the four endpoints. If one of the tests was not significant at the 0.05α level, for example evening PEFR for combination product vs. fluticasone alone, then the subsequent test (i.e. evening PEFR for combination product vs. formoterol alone) could be evaluated at the 0.025α level, however all formal testing of the remaining secondary endpoints was suspended. Similarly, if statistical significance was not reached for either



*p ≤0.05 versus fluticasone/formoterol 250/10 µg b.i.d. treatment group.
Baseline means were 2.085 L, 2.134 L, 2.143 L, and 2.066 L for the fluticasone/formoterol 250/10 µg b.i.d., fluticasone, formoterol, and placebo treatment groups, respectively, for all patients in the full analysis set.
b.i.d. = twice daily

Figure 4 Mean change in FEV_1 (L) from pre-dose at baseline to 2 h post-dose at weeks 2, 4, 8, and 12: the contribution from the formoterol component of fluticasone component of fluticasone/formoterol 250/10 µg b.i.d. combination therapy, full analysis set using last observation carried forward imputation.



p-value based on stratified log-rank test adjusting for baseline FEV_1 % predicted categories.
b.i.d. = twice daily

Figure 5 Time to discontinuations due to lack of efficacy, full analysis set.

comparator, for example for either fluticasone or formoterol alone, then all of the remaining confirmatory sequential testing was also formally suspended.

If the sequential gatekeeper approach for each of the three comparative tests was statistically significant for each of the four secondary endpoints, then confirmatory sequential testing of the remaining endpoints was carried out in the following order, using the same methodology and comparative sequence as described above, for the mean change from baseline to week 12: the percentage of symptom-free days, percentage of rescue medication-free days, percentage of asthma control days, the proportion of patients with treatment-emergent asthma exacerbations, sleep disturbance scores, and percentage of awakening-free nights.

Table 3 Mean change in morning and evening PEFR (L/Min) from baseline to week 12, full analysis set.

	Treatment group			
	Fluticasone/Formoterol 250/10 µg b.i.d. N = 108	Placebo b.i.d. N = 105	Fluticasone 250 µg b.i.d. N = 109	Formoterol 10 µg b.i.d. N = 110
AM PEFR (L/min)[a]	n = 103	n = 104	n = 104	n = 109
Baseline[b] Mean (SD)	348.3 (84.13)	343.9 (87.71)	344.9 (96.01)	338.9 (88.12)
Change from baseline to week 12 LS Mean (SE)	28.367 (5.256)	−12.567 (5.103)	12.472 (5.052)	0.713 (4.934)
Difference from fluticasone/formoterol 250/10 µg b.i.d.				
LS Mean (SE)		40.934 (6.830)	15.894 (6.915)	27.654 (6.757)
95% CI		27.501, 54.367	2.295, 29.494	14.365, 40.942
p-value		<0.001[c]	0.022[c]	<0.001[c]
PM PEFR (L/min)[a]	n = 103	n = 104	n = 105	n = 108
Baseline[b] Mean (SD)	358.4 (85.56)	351.7 (86.78)	352.4 (93.65)	348.1 (87.87)
Change from baseline to week 12 LS Mean (SE)	23.847 (4.902)	−13.770 (4.758)	10.646 (4.691)	−4.426 (4.610)
Difference from fluticasone/formoterol 250/10 µg b.i.d.				
LS Mean (SE)		37.618 (6.370)	13.201 (6.419)	28.273 (6.315)
95% CI		25.090, 50.145	0.576, 25.827	15.853, 40.694
p-value		<0.001[c]	0.040[c]	<0.001[c]

AM = morning; PM = evening; PEFR = peak expiratory flow rate; SD = standard deviation; LS = least squares; SE = standard error; CI = confidence interval; b.i.d. = twice daily; N = number of patients in treatment group; n = number of patients with data available.

[a] LS mean, SE, CI, and *p*-value are from ANCOVA with factors for displayed treatment groups, site, and baseline FEV_1 % predicted category, with Baseline PEFR value as a continuous covariate.

[b] Baseline was the average of the highest of the 3 daily measures collected in the last 7 days prior to the first dose of study drug.

[c] Statistically significant difference versus fluticasone/formoterol 250/10 µg b.i.d. based on sequential gatekeeper approach.

There were no inferential statistical tests carried out to compare fluticasone/formoterol 250/10 μg b.i.d. and 100/10 μg b.i.d. treatment arms. Missing observed data for both the primary and secondary efficacy analyses were managed using last observation carried forward (LOCF) imputation. All tests were two-sided and *p*-values below 0.05 were considered statistically significant.

For analysis of the co-primary efficacy endpoints, a sample size of 108 patients in each of the five treatment arms (540 patients in total) would have 85% power to detect a significant difference between two treatment groups using a two-sided *t*-test with $\alpha = 0.05$, assuming a difference in FEV_1 of 0.2 L (considered as a clinically significant change) and common Standard Deviation (SD) of 0.45, and taking into account an approximate dropout rate of 15%.

Results

Overall, 1219 patients were screened and, of these, 557 patients, including 41 (7.4%) adolescents, were randomised to treatment, 381 in the United States and 176 in Europe. In total, 395 (70.9%) patients completed the study and 162 (29.1%) discontinued (Fig. 2). Treatment groups were well matched in terms of patient demographics, baseline characteristics, medical history and pulmonary function (Tables 1 and 2), with little difference between the treatment groups in terms of lung function reversibility: the median FEV_1 % predicted at baseline ranged from 20.00 to 22.70 (Table 1). Approximately 40% of patients received ICS/LABA combination therapy prior to study entry. The FAS comprised 543 patients, the PP population comprised 466 patients, and the safety population comprised 556 patients (excluding one patient who was randomised but not dosed). Mean compliance rate in the safety population across all treatment groups was 86.8%.

Primary efficacy endpoints

Treatment with fluticasone/formoterol 250/10 μg b.i.d. combination therapy demonstrated superior efficacy for all

Table 4 Overview of secondary efficacy variables. Disease control: asthma control days, rescue medication-free days, symptom-free days, and awakening-free nights: mean change from baseline to week 12, full analysis set.

	Treatment group			
Characteristic	Fluticasone/Formoterol 250/10 μg b.i.d. N = 108	Placebo b.i.d. N = 105	Fluticasone 250 μg b.i.d. N = 109	Formoterol 10 μg b.i.d. N = 110
Asthma control days (%)	n = 103	n = 101	n = 102	n = 106
Baseline[a] mean (SD)	12.9 (20.48)	11.2 (19.09)	9.8 (18.72)	10.9 (22.02)
Week 12 mean (SD)	53.8 (42.69)	27.3 (35.25)	45.2 (41.47)	39.7 (39.18)
Change to week 12				
Mean (SD)	40.9 (40.98)	16.1 (37.08)	35.4 (38.90)	28.7 (43.20)
Difference from fluticasone/formoterol 250/10 μg b.i.d.[b]				
p-value		0.001[c]	0.027[c]	0.032[c]
Rescue medication-free days (%)	n = 103	n = 104	n = 106	n = 109
Baseline[a] mean (SD)	19.8 (25.15)	17.6 (22.61)	15.2 (21.40)	21.9 (27.06)
Week 12 mean (SD)	60.4 (39.70)	34.9 (35.65)	50.6 (40.63)	47.2 (39.94)
Change to week 12				
Mean (SD)	40.6 (42.11)	17.3 (37.27)	35.5 (36.80)	25.3 (43.01)
Difference from fluticasone/formoterol 250/10 μg b.i.d.[b]				
p-value		0.009[c]	0.042[c]	0.013[c]
Symptom-free days (%)	n = 103	n = 104	n = 105	n = 108
Baseline[a] mean (SD)	24.3 (25.82)	24.3 (27.59)	20.3 (25.91)	24.5 (31.34)
Week 12 mean (SD)	61.1 (41.40)	38.6 (38.76)	53.9 (40.81)	51.8 (40.83)
Change to week 12				
Mean (SD)	36.8 (36.66)	14.3 (39.98)	33.6 (37.14)	27.4 (41.71)
Difference from fluticasone/formoterol 250/10 μg b.i.d.[b]				
p-value		0.007[c]	0.342	0.140
Awakening-free nights (%)	n = 103	n = 104	n = 104	n = 109
Baseline[a] mean (SD)	62.4 (35.36)	60.7 (31.59)	59.6 (35.34)	61.9 (34.77)
Week 12 mean (SD)	82.5 (30.27)	70.4 (34.15)	82.0 (29.94)	80.9 (28.20)
Change to week 12				
Mean (SD)	20.1 (40.74)	9.7 (38.95)	22.4 (38.91)	19.0 (37.69)
Difference from fluticasone/formoterol 250/10 μg b.i.d.[b]				
p-value		0.209	0.810	0.240

N = number of patients in treatment group, n = number of patients with data available, SD = standard deviation.

[a] Baseline was the 7-day average calculated on the last 7 days prior to the first dose of study drug.

[b] Analysis method was Cochran-Mantel-Haenszel using van Elteren's method for combining Wilcoxon rank sum test results from independent strata, with baseline FEV_1 % predicted category and site as the strata for the analysis.

[c] $p \leq 0.050$ versus fluticasone/formoterol 250/10 μg b.i.d. but not statistically significant per sequential gatekeeping approach.

three co-primary endpoints (Table 2; Figs. 3–5). The contribution of the fluticasone component from the combination therapy, as analysed by the mean change in FEV_1 from pre-dose at baseline to pre-dose at week 12, demonstrated statistically significant improvements for fluticasone/formoterol compared with formoterol alone (LS mean treatment difference = 0.189 L; $p < 0.001$; Table 2). Similarly, the contribution of the formoterol component of the combination therapy, as analysed by the mean change in FEV_1 from pre-dose at baseline to 2 h post-dose at week 12, demonstrated statistically significant improvements for fluticasone/formoterol compared with fluticasone alone (LS mean treatment difference = 0.146 L; $p = 0.006$; Table 2). The improvements in pre-dose FEV_1 (Fig. 3) and 2-h post-dose FEV_1 (Fig. 4) throughout the study period for treatment with fluticasone/formoterol 250/10 μg, fluticasone, formoterol, and placebo are illustrated by the pulmonary function tests carried out at Weeks 2, 4, 8, and 12.

The fluticasone/formoterol 250/10 μg b.i.d. combination therapy was also superior to placebo with respect to the time to discontinuation due to lack of efficacy (due either to asthma exacerbation or to loss of asthma control; log-rank $p < 0.001$; Fig. 5). Fewer patients administered the 250/10 μg b.i.d. combination product discontinued prematurely due to lack of efficacy (11 patients, 10.2%) compared with each of the three comparator groups (fluticasone: 14 patients (12.8%); formoterol: 23 patients (20.9%); placebo: 41 (39.0%); Fig. 2).

Secondary efficacy endpoints

The secondary efficacy endpoints were evaluated according to improvements in lung function, disease control, and asthma symptoms from baseline to week 12. These results supported the superior efficacy of fluticasone/formoterol 250/10 μg b.i.d., with overall numerically greater improvements for patients administered the combination product compared with those receiving the individual components or placebo. Many of the comparisons met the criteria for statistically significant differences between the combination and each of the comparators as analysed according to the gatekeeping approach.

Lung function was assessed on the mean change in morning and evening PEFR values from baseline to week 12, and both assessments demonstrated statistically significantly greater improvements for patients receiving the combination product compared with those administered fluticasone alone, formoterol alone, and placebo (Table 3).

Table 5 Number of patients with treatment-emergent asthma exacerbations, full analysis set.

	Treatment group			
Characteristic	Fluticasone/Formoterol 250/10 μg b.i.d. N = 108	Placebo b.i.d. N = 105	Fluticasone 250 μg b.i.d. N = 109	Formoterol 10 μg b.i.d. N = 110
Any asthma exacerbation (%)	26 (24.1)	54 (51.4)	30 (27.5)	48 (43.6)
Odds ratio[a]		3.40	1.19	2.48
95% CI		1.88, 6.12	0.64, 2.20	1.38, 4.45
p-value[a]		<0.001[f]	0.030[f]	0.055
Any mild to moderate asthma exacerbation[b] n (%)	24 (22.2)	38 (36.2)	26 (23.9)	35 (31.8)
Odds ratio[a]		1.99	1.09	1.64
95% CI		1.09, 3.66	0.58, 2.06	0.89, 3.02
p-value[a,c]		0.040	0.229	0.329
Any severe asthma exacerbation[d] n (%)	4 (3.7)	24 (22.9)	5 (4.6)	16 (14.5)
Odds ratio[a]		7.84	1.24	4.48
95% CI		2.60, 23.60	0.32, 4.75	1.44, 13.92
p-value[a,c]		<0.001	0.054	0.042
Time to first asthma exacerbation (weeks)				
Median	1.55	2.00	1.95	2.95
p-value[e,c]		<0.001	0.575	0.002
Time to first severe asthma exacerbation (weeks)				
Median	4.30	3.50	4.10	3.00
p-value[e,c]		<0.001	0.740	0.004

N = number of patients in treatment group; n = number of patients with data available; CI = confidence interval; b.i.d. = twice daily.

[a] Odds ratio, 95% CI and *p*-value for fluticasone/formoterol 250/10 μg b.i.d. versus comparator from logistic regression model with factors for treatment group and baseline FEV_1 % predicted category.

[b] Defined as pre-dose morning PEFR >30% below baseline, or awakening at night due to asthma for ≥2 consecutive days, or use of additional rescue albuterol/salbutamol pMDI >3 inhalations per day with respect to baseline for ≥2 consecutive days.

[c] These endpoints were tertiary and *p*-values were not controlled for multiple testing.

[d] Defined as deterioration in asthma requiring additional therapy, i.e. systemic steroid, or emergency visit or hospitalisation due to asthma.

[e] Log-rank test was used to compare fluticasone/formoterol 250/10 μg b.i.d. versus comparator for survival analyses using Kaplan–Meier method.

[f] $p \leq 0.050$ versus fluticasone/formoterol 250/10 μg b.i.d. but not statistically significant per sequential gatekeeping approach.

Disease control was evaluated using asthma control days, rescue medication-free days, symptom-free days, awakening-free nights (Table 4) and asthma exacerbations (Table 5). Fluticasone/formoterol 250/10 μg b.i.d. combination therapy demonstrated numerically greater improvements for each measure of disease control, with the exception of awakening-free nights, however, none of the treatment differences between the combination product and the individual components or placebo was considered statistically significant based on the sequential gatekeeper approach.

Evaluations of asthma symptoms were assessed according to inhalations/day of rescue medication, asthma symptom scores and sleep disturbance scores obtained from patient diaries. Fluticasone/formoterol 250/10 μg b.i.d. combination therapy demonstrated numerically greater improvements compared to the individual components and placebo, with the exception of sleep disturbance scores versus fluticasone (Table 6). There were statistically significant treatment differences in measures of rescue medication use (inhalations/day) for the combination product compared with formoterol and placebo, and in asthma symptom scores compared with placebo, based on the sequential gatekeeping approach (Table 6).

Table 7 shows the 12-h serial FEV_1 AUC evaluation, based on a subgroup of 282 patients. Summary statistics show that the mean 12-h FEV_1 AUC was numerically greater for the combination product than fluticasone at weeks 0, 2, and 12. The mean changes from pre-dose at baseline over 12 h at week 0 (post first dose) and at week 12 are presented in Fig. 6a and b, respectively.

The results for the fluticasone/formoterol 100/10 μg b.i.d. treatment group were comparable with those of the 250/10 μg b.i.d. dose treatment groups for the two spirometric co-primary endpoints, the secondary endpoints, and the number of asthma exacerbations reported by patients.

Safety and tolerability

Overall, 556 randomised patients were included in the safety population and had a mean duration of study drug exposure of 10.2 weeks. The overview of adverse events reported by patients in each of the treatment arms, including the

Table 6 Overview of secondary efficacy variables. Asthma symptoms: use of rescue medication (inhalations/day), asthma symptom scores, and sleep disturbance scores: mean change from baseline to week 12, full analysis set.

	Treatment group			
Characteristic	Fluticasone/Formoterol 250/10 μg b.i.d. N = 108	Placebo b.i.d. N = 105	Fluticasone 250 μg b.i.d. N = 109	Formoterol 10 μg b.i.d. N = 110
Rescue medication use (inhalations/day)	n = 103	n = 104	n = 106	n = 109
Baseline[a] mean (SD)	2.8 (1.63)	2.9 (1.70)	3.1 (1.81)	2.8 (1.94)
Change to week 12				
Mean (SE)[b]	−1.188 (0.217)	0.107 (0.211)	−1.122 (0.207)	−0.484 (0.203)
Difference from fluticasone/formoterol 250/10 μg b.i.d.[b]				
LS Mean (SE)		−1.295 (0.282)	−0.066 (0.285)	−0.704 (0.279)
95% CI		−1.850, −0.740	−0.626, 0.494	−1.253, −0.155
p-value		<0.001[c]	0.817	0.012[c]
Asthma symptom scores	n = 103	n = 104	n = 105	n = 108
Baseline[a] mean (SD)	1.0 (0.48)	1.1 (0.66)	1.2 (0.58)	1.1 (0.70)
Change to week 12				
Mean (SE)[b]	−0.496 (0.069)	−0.081 (0.067)	−0.406 (0.066)	−0.267 (0.065)
Difference from fluticasone/formoterol 250/10 μg b.i.d.[b]				
LS Mean (SE)		−0.414 (0.090)	−0.090 (0.091)	−0.229 (0.089)
95% CI		−0.592, −0.237	−0.269, 0.089	−0.405, −0.053
p-value		<0.001[c]	0.324	0.011[d]
Sleep disturbance scores	n = 103	n = 104	n = 104	n = 109
Baseline[a] mean (SD)	0.4 (0.46)	0.5 (0.46)	0.5 (0.51)	0.5 (0.50)
Change to week 12				
LS Mean (SE)[b]	−0.193 (0.043)	−0.043 (0.042)	−0.216 (0.042)	−0.163 (0.041)
Difference from fluticasone/formoterol 250/10 μg b.i.d.[b]				
LS Mean (SE)		−0.150 (0.056)	0.023 (0.057)	−0.030 (0.056)
95% CI		−0.261, −0.039	−0.090, 0.135	−0.140, 0.080
p-value		0.008[d]	0.690	0.594

N = number of patients in treatment group; n = number of patients with data available; CI = confidence interval; LS = least squares; SD = standard deviation; SE = standard error; b.i.d. = twice daily.

[a] Baseline was the 7-day average calculated in the last 7 days prior to the first dose of study drug.

[b] LS mean, SE, CI and *p*-value are from ANCOVA with factors for treatment group, site, and baseline FEV_1 % predicted category, with baseline value as a continuous covariate.

[c] $p \leq 0.050$ versus fluticasone/formoterol 250/10 μg b.i.d. and statistically significant per sequential gatekeeping approach.

[d] $p \leq 0.050$ versus fluticasone/formoterol 250/10 μg b.i.d. but not statistically significant per sequential gatekeeping approach.

Table 7 12-h serial FEV_1 AUC (L-hour), AUC population using observed data.

	Treatment group			
FEV_1 AUC[a]	Fluticasone/Formoterol 250/10 μg b.i.d. N = 73	Fluticasone 250 μg b.i.d. N = 71	Formoterol 10 μg b.i.d. N = 71	Placebo b.i.d. N = 67
Week 0 (After first dose), n	73	71	71	67
Mean (SD)	0.295 (0.2566)	0.097 (0.2156)	0.303 (0.2554)	0.145 (0.2713)
Median	0.266	0.070	0.295	0.075
Min—Max	−0.44, 1.05	−0.36, 0.65	−0.29, 1.19	−0.41, 1.03
Week 2, n	69	68	67	61
Mean (SD)	0.316 (0.2821)	0.206 (0.3062)	0.214 (0.3061)	0.064 (0.3144)
Median	0.302	0.144	0.194	−0.006
Min—Max	−0.26, 1,21	−0.36, 1.30	−0.87, 1.17	−0.69, 1.01
Week 12, n	65	65	54	48
Mean (SD)	0.311 (0.2815)	0.203 (0.3355)	0.229 (0.3428)	0.093 (0.3814)
Median	0.281	0.146	0.206	0.022
Min—Max	−0.35, 1.09	−0.68, 1.19	−0.61, 1.23	−0.51, 1.15

N = number of patients in treatment group; n = number of patients with data available; AUC = area under the curve; FEV_1 = forced expiratory volume in the first second; Max = maximum; Min = minimum; SD = standard deviation.

[a] At each visit, AUC calculated only in case of at least 4 measured post-dose FEV_1 values. AUC calculated using the linear trapezoidal rule: the area between 2 consecutive time points was calculated as [(time 2 − time 1) * (change at time 1 + change at time 2)]/2. The areas were summed and time weighted for the 12 h.

number of events considered by the Investigator to be at least possibly related to study medication, is summarised in Table 8. Adverse events were predominantly mild or moderate in severity. Severe adverse events were reported by 59 patients (Table 9). The only severe adverse event noted in more than one patient was asthma, as reported by 3 (2.7%) patients in the fluticasone/formoterol 250/10 μg b.i.d. group; 5 (4.4%) patients in the fluticasone/formoterol 100/10 μg b.i.d. group; 6 (5.3%) in the fluticasone group; 16 (14.4%) in the formoterol group, and 21 (19.3%) patients in the placebo group. The most frequently reported adverse events were asthma, nasopharyngitis, and upper respiratory tract infection (Table 9), adverse events, which are all typical of this type of treatment.[43] Study medication-related oral candidiasis was only observed in two patients (1.8%) in the fluticasone treatment group, and dysphonia for one patient administered fluticasone/formoterol 100/10 μg b.i.d.. Serious adverse events were experienced by 6 patients (1 administered fluticasone/formoterol 250/10 μg b.i.d.; 2 administered fluticasone/formoterol 100/10 μg b.i.d.; 2 in the fluticasone group, and one in the formoterol group), none of which were considered by the Investigator to be study medication related. No deaths were reported. Overall, there were no significant differences in adverse events between treatment groups.

There were no clinically relevant changes or group differences for laboratory values, vital signs, or ECG parameters.

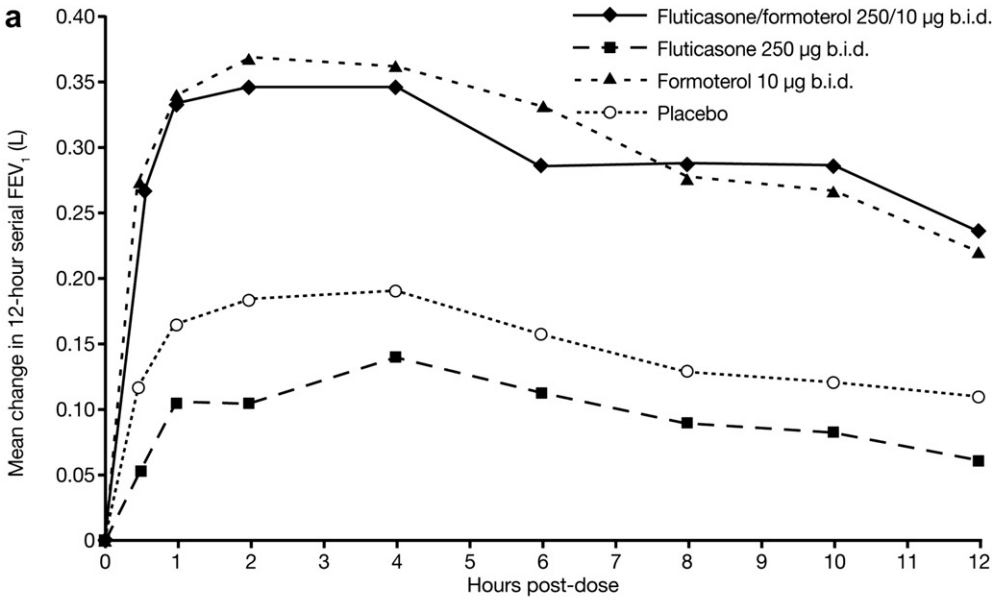
Discussion

This study compared the efficacy and safety of fluticasone/formoterol 250/10 μg b.i.d. with the individual components administered alone, and placebo, over a 12 week study period. The study population consisted of adolescents and adults with moderate-to-severe asthma (FEV_1 40—80% of predicted normal values; FEV_1 reversibility ≥14.5%) who required inhaled corticosteroid therapy prior to screening.

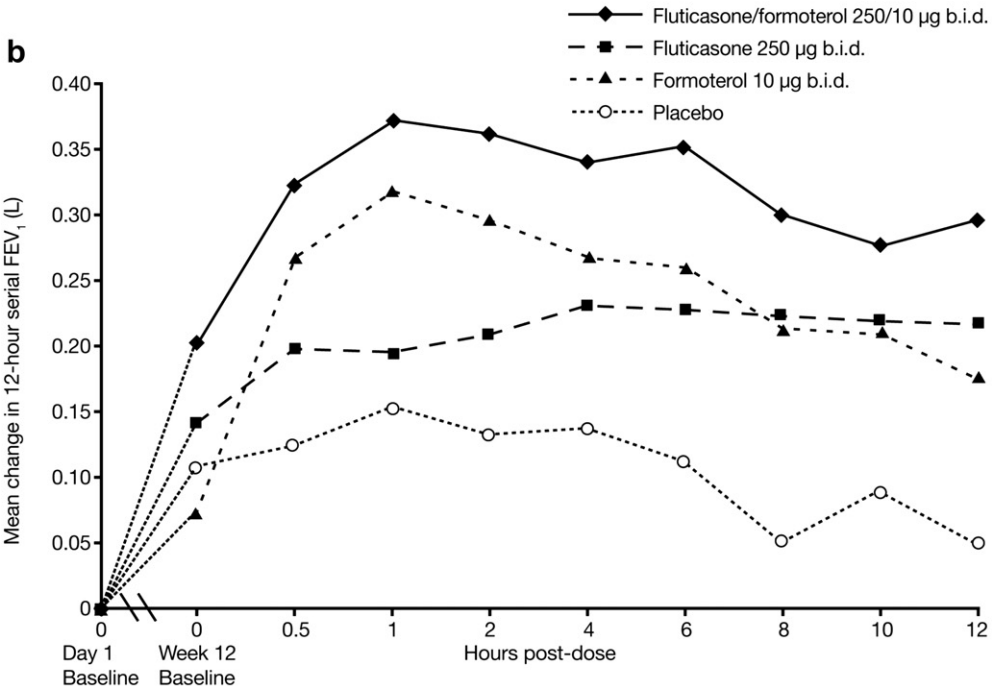
The three co-primary efficacy endpoints showed that fluticasone/formoterol 250/10 μg b.i.d. was superior compared with each of the individual ICS and LABA components administered separately, and placebo. The clinically important and statistically significant difference between fluticasone/formoterol 250/10 μg b.i.d. and formoterol for the change in FEV_1 from pre-dose at baseline to pre-dose at week 12 showed the contribution of the fluticasone component of the combination. The difference between fluticasone/formoterol 250/10 μg b.i.d. and fluticasone for mean change in FEV_1 from pre-dose at baseline to 2 h post-dose at week 12 demonstrated the contribution from the formoterol component. Fluticasone/formoterol 250/10 μg b.i.d. was also shown to be superior to placebo for time to discontinuation due to lack of efficacy. Increases in 12-h serial FEV_1 were seen with formoterol and the fluticasone/formoterol 250/10 μg b.i.d. combination following the first treatment dose, as expected with a LABA, whereas fluticasone, which would not be expected to have had an effect at this time, showed similar changes in serial FEV_1 to those with placebo. Importantly, after 12 weeks of treatment, the effects of fluticasone on 12-h serial FEV_1 were greater than those of placebo, although they were smaller than those of fluticasone/formoterol.

The improvements in FEV_1 were experienced by patients shortly after treatment initiation (week 2) with fluticasone/formoterol 250/10 μg b.i.d. and were sustained over the 12-week treatment period. This was supported by the patient-recorded PEFR data, which showed statistically significant differences in the changes from baseline to week 12 between the 250/10 μg b.i.d. combination and the comparator groups. The mean 12-h FEV_1 AUC of fluticasone/formoterol 250/10 μg b.i.d. was also numerically greater than that for fluticasone throughout the treatment period.

These results are consistent with findings from studies comparing other single-inhaler ICS/LABA combinations with



At 0.5, 1, 2, 4, 6, 8, 10, and 12 hours post-dose, samples sizes were 73, 72, 73, 73, 73, 73, 72, and 72, respectively, in the fluticasone/formoterol 250/10 µg b.i.d. group; 71, 69, 71, 71, 71, 71, 69, and 70, respectively, in the fluticasone 250 µg b.i.d. group; 70, 71, 70, 70, 71, 71, 70, and 71, respectively, in the formoterol group, and 67, 67, 67, 67, 67, 65, 67, and 67, respectively, in the placebo group.
b.i.d. = twice daily



At 0.5, 1, 2, 4, 6, 8, 10, and 12 hours post-dose, samples sizes were 65, 64, 65, 65, 62, 63, 62, and 61, respectively, in the fluticasone/formoterol 250/10 µg b.i.d. group; 65, 65, 65, 65, 61, 59, 59, and 59, respectively, in the fluticasone group; 54, 51, 54, 54, 49, 49, 47, and 48, respectively, in the formoterol group, and 48, 48, 48, 48, 42, 42, 42, and 42, respectively, in the placebo group.
b.i.d. = twice daily

Figure 6 Mean change from pre-dose at baseline in 12-h serial FEV_1 (L) after (a) the first dose at week 0 and (b) 12 weeks of treatment, 12-h serial FEV_1 analysis set using observed data.

their individual component therapies.[44–46] Fluticasone/salmeterol and budesonide/formoterol combinations have each shown significantly greater improvements in FEV_1 and PEFR, and significantly longer time to withdrawal because of worsening asthma, compared with individual monotherapies and placebo in 12-week studies in patients who were previously receiving inhaled corticosteroids therapy.[18,47,48] Similarly, beclometasone/formoterol has demonstrated

Table 8 Overview of patients with treatment-emergent adverse events, safety population.

	Number (%) of patients				
	Fluticasone/Formoterol 250/10 μg b.i.d. N = 110	Fluticasone 250 μg b.i.d. N = 113	Formoterol 10 μg b.i.d. N = 111	Fluticasone/Formoterol 100/10 μg b.i.d. N = 113	Placebo b.i.d. N = 109
Any adverse event	34 (30.9)	48 (42.5)	39 (35.1)	42 (37.2)	52 (47.7)
Any serious adverse event	1 (0.9)	2 (1.8)	1 (0.9)	2 (1.8)	0 (0.0)
Any severe adverse event	4 (3.6)	9 (8.0)	17 (15.3)	8 (7.1)	21 (19.3)
Any adverse event leading to study discontinuation[a]	4 (3.6)	9 (8.0)	17 (15.3)	5 (4.4)	26 (23.9)
Any adverse event with probable or possible relationship to study drug	7 (6.4)	11 (9.7)	12 (10.8)	3 (2.7)	20 (18.3)
Any adverse event leading to death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[a] Three of the 61 patients (1 fluticasone/formoterol 250/10 μg b.i.d., 1 fluticasone, and 1 placebo) had adverse event reported as the primary reason for early discontinuation. Two (1 fluticasone, 1 placebo) of the 61 patients had adverse event reported as primary reason for early discontinuation from study. An additional 55 patients (3 fluticasone/formoterol 250/10 μg b.i.d., 5 fluticasone/formoterol 100/10 μg b.i.d., 7 fluticasone, 16 formoterol, and 24 placebo) had lack of efficacy reported as the primary reason for early discontinuation from the study, and had adverse events reported with "study therapy permanently stopped" as an action taken. In addition, the adverse event for 1 formoterol patient was reported on Day 84 (Week 12 Visit) and thus, the patinet was considered to have completed the study.

superiority to beclometasone dipropionate alone for measures of lung function, including morning PEFR and FEV_1, in patients with moderate-to-severe asthma over 24 weeks' treatment.[22]

The multiple secondary endpoints used to measure disease control and asthma symptoms, evaluated using the gatekeeper methodology, showed clinically important improvements throughout the course of the study for patients receiving 250/10 μg b.i.d. combination therapy. Overall, these results supported the superior efficacy of fluticasone/formoterol 250/10 μg b.i.d. compared to the each of the individual components and placebo.

Asthma control is clinically perhaps the most relevant endpoint to patients, and although it was a non-validated measure, the definition of asthma control used in this study (asthma score of 0, sleep disturbance score of 0, and no use

Table 9 Number (%) of patients with treatment-emergent adverse events reported for >2.0% of patients in any treatment group, safety population.

System organ class preferred term	Number (%) of patients				
	Fluticasone/Formoterol 250/10 μg b.i.d. N = 110	Fluticasone 250 μg b.i.d. N = 113	Formoterol 10 μg b.i.d. N = 111	Fluticasone/Formoterol 100/10 μg b.i.d. N = 113	Placebo b.i.d. N = 109
Any event	34 (30.9)	48 (42.5)	39 (35.1)	42 (37.2)	52 (47.7)
Infections and infestations	15 (13.6)	20 (17.7)	17 (15.3)	23 (20.4)	19 (17.4)
Nasopharyngitis	5 (4.5)	6 (5.3)	3 (2.7)	8 (7.1)	3 (2.8)
Upper respiratory tract infection	3 (2.7)	4 (3.5)	6 (5.4)	2 (1.8)	3 (2.8)
Sinusitis	1 (0.9)	2 (1.8)	1 (0.9)	1 (0.9)	3 (2.8)
Urinary tract infection	1 (0.9)	1 (0.9)	3 (2.7)	2 (1.8)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	6 (5.5)	13 (11.5)	22 (19.8)	12 (10.6)	28 (25.7)
Asthma[a]	4 (3.6)	6 (5.3)	18 (16.2)	6 (5.3)	25 (22.9)
Cough	2 (1.8)	1 (0.9)	1 (0.9)	3 (2.7)	1 (0.9)
Nervous system disorders	8 (7.3)	4 (3.5)	4 (3.6)	3 (2.7)	4 (3.7)
Headache	5 (4.5)	3 (2.7)	3 (2.7)	1 (0.9)	3 (2.8)
Gastrointestinal disorders	6 (5.5)	5 (4.4)	1 (0.9)	3 (2.7)	3 (2.8)
Nausea	0 (0.0)	3 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)

Note: Adverse events were coded using MedDRA version 9.0. At each level of summation (preferred term, system organ class and overall), each patient was counted only once. Percentages are based on the number of patients in the population for each treatment group.

[a] An exacerbation of asthma was considered as an adverse event if it did not resolve with the study drug, including albuterol, and additional medication was required (e.g. systemic glucocorticosteroids).

of rescue medication) is highly suggestive of a meaningful change in asthma status. Patient recorded asthma symptom scores and the proportion of asthma control days were numerically greatest for fluticasone/formoterol 250/10 μg b.i.d. compared to the monotherapies and placebo. In addition, the 250/10 μg b.i.d. combination demonstrated numerically greater effects compared to the three comparator groups for each of the constituent components of asthma control. This study was not powered for the analysis of asthma exacerbations, which would require much larger patient numbers and longer study timescales. However, patients in the 250/10 μg b.i.d. combination therapy group reported fewer exacerbations, mild-to-moderate as well as severe, compared to the other groups.

The improvements in measures of asthma control seen with the fluticasone/formoterol combination are also in line with findings for other ICS/LABA combination studies. These have also shown greater improvements in asthma exacerbations and measures of asthma control, such as symptom scores, rescue medication use, symptom-free days and awakening-free nights free, compared with their individual components.[18,22,47,48]

As well as the primary and secondary endpoints comparing fluticasone/formoterol 250/10 μg b.i.d with each of the individual components and placebo, a low dose (100/10 μg b.i.d.) combination therapy arm was included in this study. The results for the two fluticasone/formoterol treatment arms were comparable. This was as expected for fluticasone-containing treatments administered at these dose levels.[31] The flat dose-response for all currently approved classes of inhaled monotherapies in asthma is well recognised. Typically, wide dose separation is required to demonstrate differences in efficacy, i.e. for spirometry results, across a dose range for both ICSs and β_2-agonists[43,49,50] and would involve doses separated by a greater dose multiple than used here.

In conclusion, fluticasone/formoterol combination therapy demonstrated a good safety profile, similar to that of the individual components, and was well-tolerated during the 12-week treatment period. The results of this study therefore successfully demonstrated the benefits of the new fluticasone/formoterol 250/10 μg b.i.d. therapy providing superior efficacy compared to its individual components and placebo for the management of moderate to severe asthma. For such adolescent and adult patients, who require ICS/LABA therapy, fluticasone/formoterol will present an efficacious alternative treatment option.

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Conflict of interest statement

Jonathan Corren, Lyndon Mansfield, Tetyana Pertseva and Viktor Blahzko had no proprietary interest in the tested product which was the subject of this study nor did they receive any payment from the sponsor (excluding the costs of conducting the study). Kirsten Kaiser was an employee of SkyePharma which sponsored this study.

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