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Efficacy of a fixed combination of ciclesonide and formoterol: The EXCITED-study

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Summary

Recommended treatment for moderate to severe asthma is the combination of an inhaled corticosteroid and a long-acting beta2-agonist. The present study was designed to evaluate the efficacy of a newly developed fixed combination of ciclesonide and formoterol in comparison to the marketed fixed combination of fluticasone and salmeterol in patients with moderate asthma.

This was a phase II, multi-centre, randomized, parallel-group, double-blind, double-dummy study. After a 2-week run-in period, 160 patients with moderate asthma were randomized to a 6-week treatment with ciclesonide/formoterol 320/9 μg bid (CIC/F) or fluticasone propionate/salmeterol 250/50 μg bid (FP/S), both delivered as powder formulations.

The primary outcome FEV1 increased during treatment by 0.356 L in the CIC/F group and by 0.288 L in the FP/S group ($p < 0.0001$). The increases were statistically significant and clinically relevant. The between-treatment analysis demonstrated non-inferiority of CIC/F to FP/S treatment ($p < 0.0001$). A significant improvement from baseline in lung function, symptom score and rescue medication use was observed in both groups at all time points. No differences were observed between treatments in the frequency of adverse events and overnight urinary cortisol/creatinine ratio.

The studied fixed combination of ciclesonide/formoterol is not inferior to the marketed fixed combination of fluticasone/salmeterol in terms of efficacy and tolerability.

Introduction

Asthma is a chronic disease of the airways, causing recurrent episodes of symptoms, variable airflow limitation, and increased airway responsiveness. International guidelines recommend the combination of a long-acting beta2-agonist (LABA) with low-to-medium dose inhaled corticosteroids (ICS) if asthma is not fully controlled by ICS alone, as first choice treatment in moderate asthma.[1—5] Several clinical trials have shown that the addition of a LABA to ICS is more

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beneficial than increasing the dose of ICS alone in terms of symptom control and pulmonary function.[6–10] The introduction of LABA to the treatment of asthma has changed the way in which β2-agonists are used from simple rescue agents to medication that provides long lasting bronchodilation and thus reduces the need for rescue treatment. Landmark studies demonstrated that combined therapy with ICS and LABA provides better asthma control than high doses of ICS alone.[1,11] Treatment with an ICS/LABA combination in a single inhaler, with the same efficacy and safety profile as the two drugs given separately, may also produce a better adherence to anti-inflammatory treatment.[12–19] To date, several fixed ICS/LABA combination inhalers are widely used, offering improvements in control in patients with persistent asthma compared with ICS therapy alone as well as with free combinations of the same drugs.[2–4,20,21] Consequently, a combination treatment of the inhaled glucocorticosteroid ciclesonide and the long-acting beta2-agonist formoterol fumarate (abbreviated as formoterol) was developed for the treatment of persistent asthma. Ciclesonide is an effective and safe drug for the treatment of asthma. In a number of studies ciclesonide was shown to be non-inferior to fluticasone propionate (FP) and budesonide (Bud) with regard to lung function variables, improvement of asthma symptoms, and reduction of the use of rescue medication.[22–25] Formoterol belongs to a class of β2-agonists that have a fast onset and a long duration of action and are able to maintain bronchodilation for at least 12 h. As formoterol is widely used for long-term maintenance treatment of asthma and for the prevention of bronchospasm, a substantial amount of information is available on the substance.[26]

In this exploratory study the efficacy of the fixed combinations of ciclesonide and formoterol and of FP and salmeterol xinafoate (abbreviated as salmeterol) was assessed in patients with moderate asthma.

Methods

This was a 10-week, multi-centre, randomized, parallel-group, double-blind, double-dummy study. The study (EudraCT number 2004-002983-80 registered at https://www.clinicaltrialsregister.eu/) was approved by the Institutional Review Board or Independent Ethics Committee of each participating centre and was conducted in accordance with the ethical principles embodied in the Declaration of Helsinki and local applicable laws and regulations. All patients provided written informed consent prior to taking part in the study.

Selection of the study population

The study was carried out in 11 outpatient respiratory clinics in Germany and Austria. The study enrolled male and female patients aged 12–75 years with a history of asthma for at least 6 months, with an FEV1 >60% to <80% of predicted, when short-acting rescue medication was withheld for at least 6 h and patients who were in good health, with the exception of asthma. All eligible patients had to be pretreated either with a constant dose of ≤500 μg fluticasone (or equivalent) per day only, or with a constant dose of ≤250 μg fluticasone (or equivalent) per day in combination with an inhaled LABA in a fixed or free combination, or sustained-release theophylline, or a leukotriene antagonist, or a lipoxygenase inhibitor, or inhaled anticholinergics, or an oral β-agonist, or inhaled disodium cromoglycate, or inhaled nedocromil during at least four weeks prior to entry into the study. After the run-in period (two weeks) patients were randomized to study drug if they demonstrated reversibility by ΔFEV1 ≥15% after inhalation of 200–400 μg salbutamol or, if during run-in reversibility was not achieved, diurnal PEF variation ≥15% during at least three days within the last seven days of the run-in period. Additionally, asthma symptoms had to occur more than once a week, but less than once a day.

Patients with COPD and/or other relevant lung diseases causing alternating impairment in pulmonary function, current smokers or ex-smokers for ≤6 months or a smoking history of ≥10 cigarette pack years and patients using systemic glucocorticosteroids within 2 months prior to entry into the study, or more than 3 courses during the last 6 months were excluded.

Study treatments and design

Study drugs were a newly developed fixed combination of 320 μg ciclesonide and 9 μg formoterol and the marketed salmeterol/fluticasone fixed combination (50 μg/250 μg), both formulated as a powder. The appropriate dosing of the new CIC/F compound was estimated based on phase I safety data and the fine particle fraction of the new powder formulation which is approximately 50% smaller than that of the ciclesonide hydrofluoroalkane metered-dose inhaler (HFA MDI).

The study protocol comprised a screening visit, a 14-day run-in period (patients continued their previous asthma medication), a 6-week treatment period, and a follow-up period (Fig. 1). Patients were allowed to use salbutamol as rescue medication throughout the study. At visit 2 eligible patients were randomized to treatment with ciclesonide/formoterol 320/9 μg bid (total daily dose of ciclesonide 640 μg, formoterol 18 μg (CIC/F)) or fluticasone propionate/salmeterol 250/50 μg bid (total daily dose of fluticasone 500 μg, salmeterol 100 μg (FP/S)) (ratio 1:1). Randomization was in balance-block design by investigational centre. Patients received the study medication using two different DPIs: one Ultrahaler® and one Diskus®. Due to the double-dummy technique and the code labelling, neither the patient nor the investigator or anyone else involved in the study knew throughout the study whether CIC640/F18 or FP500/S100 was administered during the treatment period.

Lung function (FEV1: forced expiratory volume in 1 s, FVC: forced vital capacity, FEF25-75%: mean forced expiratory flow between 25% and 75% of vital capacity) was measured at visits 1, 2 (baseline), 3, and 4. Throughout the study patients recorded their morning and evening PEF (peak expiratory flow), use of rescue medication, and asthma-related symptoms in an electronic diary. Adverse events (AEs) and use of concomitant medication were documented by the investigator throughout the study. At study visits 1, 3, 4, and a follow-up visit (if applicable)

standard laboratory investigations were carried out. Urine free cortisol (24-h) was determined at visits 1 and 4. Physical examination (including vital signs) and assessment of skin bruising were performed at every study visit. ECG was recorded at visits 1, 3, and 4.

Protocol outcome measures

The primary efficacy variable was the difference in FEV1 (L) between the last available valid visit (up to visit 4) and visit 2. The co-primary efficacy variable was the percentage of days without asthma symptoms and use of rescue medication (%) (diary, last four weeks during treatment compared with the two run-in weeks).

At each study visit, FEV1, FVC, and FEF25-75% (triplicate) were recorded. Individual spirograms were checked by the investigator for acceptability and reproducibility.[27] Before pulmonary function tests (PFT) rescue medication had to be withheld for at least 6 h. PFT was performed in accordance with standard procedure,[28] at each visit before the intake of the morning dosage of baseline or study medication, meaning that the morning dose of study drug was taken onsite after PFT under the investigator's supervision and proper inhaler technique was checked.

To assess reversibility the patient inhaled 200 μg salbutamol after initial lung PFT. Triplicate lung function measurements were repeated after 15 min. In case of insufficient response (ΔFEV1 $< 15\%$ of initial), another dose of 200 μg salbutamol was inhaled and further FEV1 readings obtained 15 min thereafter. It was also acceptable to administer 400 μg salbutamol in one dose after initial PFT and perform just one set of triplicate PFT after 15 min.

Patients recorded PEF using an electronic PEF metre (AM2+, VIASYS) daily in the morning immediately after getting up and in the evening before going to bed. Readings were done more than 6 h after use of rescue medication and before inhalation of baseline and study medication. At each home measurement, three readings were obtained and recorded in the diary; the highest value was used for evaluation. Diurnal PEF fluctuation was calculated by the electronic PEF metre. The highest morning and the highest evening value from the same day were selected.

Additional study parameters included nighttime and daytime asthma symptoms and the daily use of rescue medication (salbutamol), assessed on a daily basis by the patient in the diary of the electronic PEF metre. Asthma exacerbation or lack of efficacy was defined as increasing asthma symptoms or a distinct drop in lung function (e.g. decrease in morning PEF on two consecutive days by more than 30% below the best value recorded during the baseline period) requiring treatment with oral glucocorticosteroids. If an asthma exacerbation occurred during the study the patient was withdrawn from further participation and treated according to individual needs.
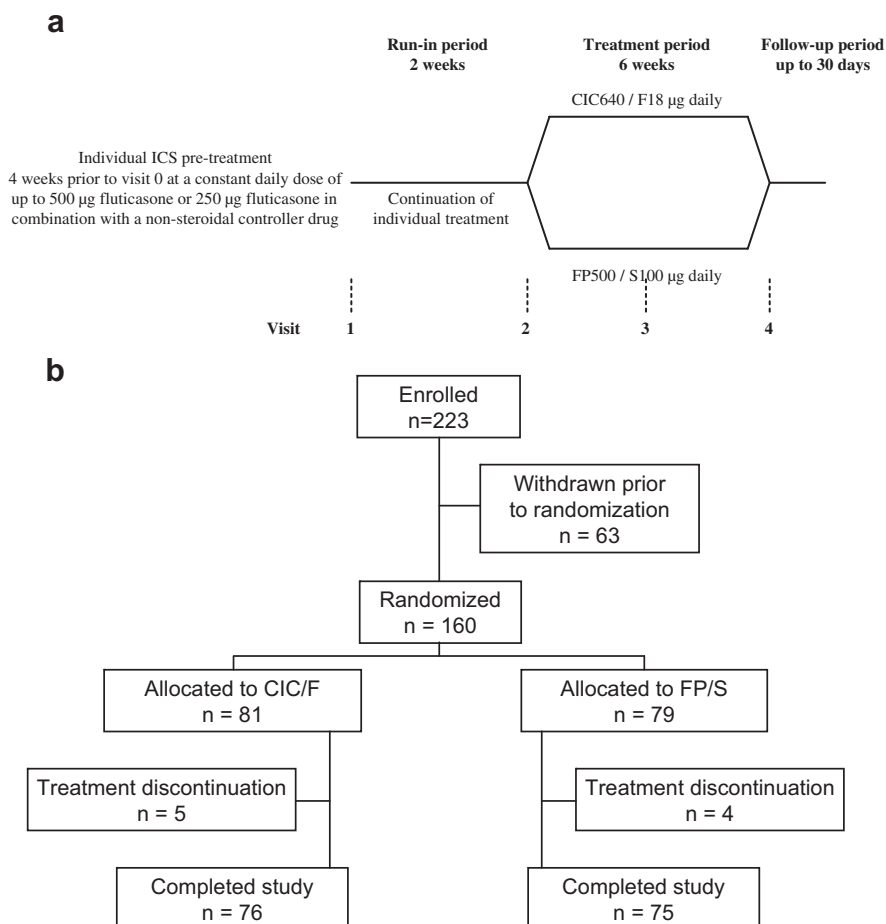

Figure 1 a) Study flow chart. b) Patient flow chart.

Safety assessments included recording of adverse events (AEs) and serious adverse events (SAEs), collection of clinical laboratory data for haematology and blood chemistry, monitoring of vital signs, electrocardiogram (ECG), and oropharyngeal examinations. The intensity of AEs was assessed as being mild, moderate or severe. Suspected oral candidiasis had to be confirmed by a swab culture.

A list of secondary variables is available as part of the online repository.

Statistics

Spirometric lung function variables as well as morning and evening PEF from diary were analyzed with an ANCOVA (analysis of covariance). The dependent variable was the difference of the values of visits after randomization to the value at visit 2. Besides the treatment, the following factors and covariates (all fixed) were included in the model: value at visit 2, age, sex, and country (Germany and Austria), more so as the 2 populations differ in median age. However, baseline values of FEV1 (absolute and percent predicted) match very well in both groups irrespective of age. To overcome the problem that age (or other covariates) may have a significant impact on the outcome of the trial the ANCOVA model included age as covariate and treatment least square means are presented.

No interaction term was included in this model, which was used to test both within- and between-treatment differences. With regard to the primary variable FEV1, the comparison between treatments was based on the difference between visit 4 or the last available measurement during treatment (PP (per protocol) analysis) and the baseline value at randomization (visit 2), while for the co-primary variable percent days without asthma symptoms and use of rescue medication it was based on the difference between I_{last} (interval of the last four treatment weeks, mITT (modified intention-to-treat) analysis) and I_{run-in} (run-in interval, two weeks before visit 2). The mITT corresponds to ITT analysis but conducted "as treated" (not "as randomized"). The non-inferiority acceptance limit for FEV1 was −0.200 L. An additional repeated measurement model was analyzed to investigate the robustness of the results of the endpoint analysis.

Diurnal PEF fluctuation, asthma symptom scores, use of rescue medication, and asthma control variables were analyzed non-parametrically. Within-group differences were analyzed with Pratt's modification of Wilcoxon's signed rank test; between-treatment comparisons were analyzed with the Mann–Whitney U test. The difference between treatments with respect to the frequency of local oropharyngeal AEs was analyzed by means of Fisher's exact test. Between-treatment differences of urine free cortisol variables were analyzed with the nonparametric van Elteren test, stratified by centre pool. Descriptive statistics are given for AEs, laboratory variables, and vital signs. A sample size of $n = 75$ randomized patients per group was primarily chosen on grounds of feasibility, resulting in ca. 60 patients per group in the PP analysis. This gave a power of 77% to demonstrate non-inferiority with regard to FEV1 for a common standard deviation of 400 mL and no between-treatment difference at the one-sided 2.5% level confirmed by nQuery, version 7. All analyses are PP, confirmed by mITT.

Results

One hundred and sixty patients with moderate asthma were randomized and included in the full analysis set ($N = 81$ CIC/F and $N = 79$ FP/S). Baseline data (Table 1) of the two groups were comparable though patients in the CIC/F group tended to be younger than those in the FP/S group (median of 44 and 51 years, respectively).

Efficacy results

Lung function
The primary outcome parameter FEV1 increased significantly and clinically relevant by 0.356 L in the CIC/F group and by 0.288 L in the FP/S group during the treatment period (Fig. 2, Table 2). The between-treatment analysis demonstrated non-inferiority of CIC/F to FP/S treatment (non-inferiority margin −0.200 L). As non-inferiority of CIC/F to FP/S was shown for the primary variable, the co-primary variable patient perceived asthma control (based on symptoms and use of rescue medication) was tested subsequently for difference between CIC/F and FP/S with a confirmatory intention. Improvements in asthma control were observed in both treatment groups (Table 3), with no statistically significant difference between treatments. For FVC a statistically significant increase occurred in both treatment groups (Table 2), with non-inferiority of CIC/F to FP/S also demonstrated for FVC (non-inferiority margin −0.200 L). Repeated measurement analysis of FEV1, FVC, and FEF25−75% confirmed the results of the endpoint analyses.

Morning and evening PEF from diary increased statistically significantly in both treatment groups (CIC/F morning/evening change in PEF compared to baseline (LSMean ± SE) 20.7 ± 7.8, $p = 0.0088$/19.5 ± 7.4, $p = 0.0097$; FP/S 19.5 ± 7.9, $p = 0.0146$/15.6 ± 7.5, $p = 0.0399$; Fig. 2b). Between-treatment comparisons demonstrated non-inferiority of CIC/F to FP/S for both variables (non-inferiority margin −25 L/min). PEF variability decreased statistically significantly during treatment with CIC/F only, while there was no statistically significant difference between treatments.

Asthma symptoms
Asthma symptom scores (total, daytime, and nighttime) decreased statistically significantly with both treatments (CIC/F decrease sum (Hodges-Lehmann point estimate) −0.43, $p < 0.0001$; FP/S −0.42, $p < 0.0001$), with no statistically significant difference between the two treatments. Comparable improvements were seen for the use of rescue medication and the percentage of asthma symptom-, rescue medication-, and nocturnal awakening-free days.

Safety results

Adverse events
During the treatment period 37 (45.7%) patients in the CIC/F group experienced 60 AEs and 29 (36.7%) patients in the

FP/S group experienced 41 AEs. The most frequently reported AEs belonged to the system organ class infections. Within this class, oral candidiasis was the most common AE, reported by six patients in each treatment group. The majority of AEs was moderate in intensity in both treatment groups. No severe AEs were reported. The number of AEs assessed by the investigator as likely related to study medication was comparable in both treatment groups (14.8% of patients in the CIC/F group and 12.7% in the FP/S group). Only one patient in the CIC/F group experienced AEs that were assessed as definitely related by the investigator (asthenia and tremor). Two patients in the CIC/F group experienced treatment-emergent AEs related to cardiac disorders. The events were non-serious, mild (cardiovascular disorder, AE verbatim: circulatory disturbance) and moderate (atrial fibrillation and tachycardia) in intensity and both patients recovered without sequelae. The investigator assessed the tachycardia and the atrial fibrillation as likely related to the intake of study medication; the cardiovascular disorder was assessed as unrelated.

No death occurred during the study and only one SAE ('loose body in joint') was reported in the CIC/F group (patient was hospitalized for this SAE). The patient did not discontinue the study and the SAE was assessed as unrelated to study medication by the investigator. The patient recovered from the SAE without sequelae five days after onset. Three patients in the CIC/F group and two patients in the FP/S group discontinued the study due to an AE. None of these AEs were serious or severe in intensity.

Clinical laboratory

There were no clinically relevant changes in laboratory values over time in any of the treatment groups. Nine patients in the CIC/F and seven patients in the FP/S group reported AEs associated with abnormal laboratory values. They were all mild or moderate in intensity and assessed by the investigator as unrelated or unlikely related, apart from one incidence of increased blood glucose in the FP/S group, which was likely related to study medication.

Urine free cortisol adjusted for creatinine remained unchanged during treatment with CIC/F, while it decreased statistically significantly in the FP/S group ($p = 0.0277$, restricted SAF, confirmed by the full analysis set). Between treatments no statistically significant difference was observed.

Physical examination and vital signs

Physical examination, blood pressure, and heart ratio measured at site visits during the study period did not reveal any influence of the two different treatments. Due to the small number of skin bruises, analysis was omitted. Only one clinically relevant finding was recorded on ECG data: one patient had intermittent atrial fibrillation at visit 4, which was reported as an AE (see above).

Table 1 Demographic and other baseline characteristics.

Demographic characteristics		FAS		VCS	
		CIC640/F18 (N = 81)	FP500/S100 (N = 79)	CIC640/F18 (N = 67)	FP500/S100 (N = 68)
Age (years)	Median (range)	44 (12, 71)	51 (12, 75)	43 (12, 71)	51 (12, 75)
Weight (kg)	Mean ± SD	79 ± 16	78 ± 17	79 ± 16	78 ± 17
Height (cm)	Mean ± SD	171 ± 10	169 ± 9	171 ± 10	169 ± 9
Sex (n (%))	Male	39 (48.1)	37 (46.8)	30 (44.8)	33 (48.5)
Pretreatment at visit 0 (n (%))	ICS only	17 (21.0)	12 (21.5)	14 (20.9)	15 (22.1)
	ICS and LABA	63 (77.8)	61 (77.2)	53 (79.1)	53 (77.9)
	ICS and other	1 (1.2)	1 (1.3)	NA	NA
Smoking status (n (%))	Non-smokers	53 (65.4)	58 (73.4)	44 (65.7)	49 (72.1)
	Ex-Smokers	28 (34.6)	21 (26.6)	23 (34.3)	19 (27.9)
Pack-years	Mean ± SD	5.8 ± 2.3	5.1 ± 2.4	5.8 ± 2.3	4.9 ± 2.4
FEV1 at visit 1 (L)	Mean ± SD	2.304 ± 0.540	2.226 ± 0.590	2.277 ± 0.516	2.218 ± 0.599
FEV1 (% of predicted)	Mean ± SD	70.2 ± 5.5	71.1 ± 5.5	70.3 ± 5.5	70.7 ± 5.6
FEV1 at visit 2 (L)	Mean ± SD	2.376 ± 0.535	2.269 ± 0.597	2.327 ± 0.523	2.265 ± 0.580
FEV1 at visit 2 (% of predicted)	Mean ± SD	72.5 ± 5.3	72.6 ± 5.5	71.8 ± 5.0	72.4 ± 5.2
Reversibility (% increase)	Mean ± SD	23.2 ± 7.2	20.7 ± 8.3	22.7 ± 7.0	19.5 ± 6.9
Symptome score sum at W0	Median (range)	0.7 (0.0, 2.9)	0.7 (0.0, 2.8)	0.7 (0.0, 2.7)	0.7 (0.1, 2.8)
Use of rescue medication at W0	Median (range)	1.0 (0.0, 6.4)	1.0 (0.0, 6.6)	1.0 (0.0, 5.7)	1.0 (0.0, 6.6)

Numbers and percentages are based on the number of patients with data available. FAS = full analysis set, VCS = valid cases set, CIC640/F18 = ciclesonide/formoterol 320/9 μg twice daily, FP500/S100 = fluticasone propionate/salmeterol 250/50 μg twice daily, ICS = inhaled corticosteroid, LABA = long-acting β2-agonist, visit 1 = baseline visit, visit 2 = randomization visit, W0 = week before visit 2, NA = not applicable, SD = standard deviation.

Discussion

The present clinical trial demonstrated comparable efficacy of the two fixed combinations CIC/F and FP/S in patients with moderate asthma, pre-treated with ICS alone or in combination with another asthma drug in a well controlled study design. The two treatment groups were matched in terms of asthma severity and baseline values of all outcome measures evaluated.

The populations in both treatment groups had a real potential to improve from baseline to endpoint, as demonstrated by the significant increases in lung function during the course of the study, showing real equivalence between the two study treatments. In addition, equivalence was not due to lack of efficacy for both treatments.[29] The increases in the primary efficacy variable between baseline and end of study were both statistically significant and clinically relevant in both groups, confirming that the study had the power to detect potential differences between groups. This is true although the minimum dose required to achieve asthma control was not established in the study. The results of the other pulmonary function
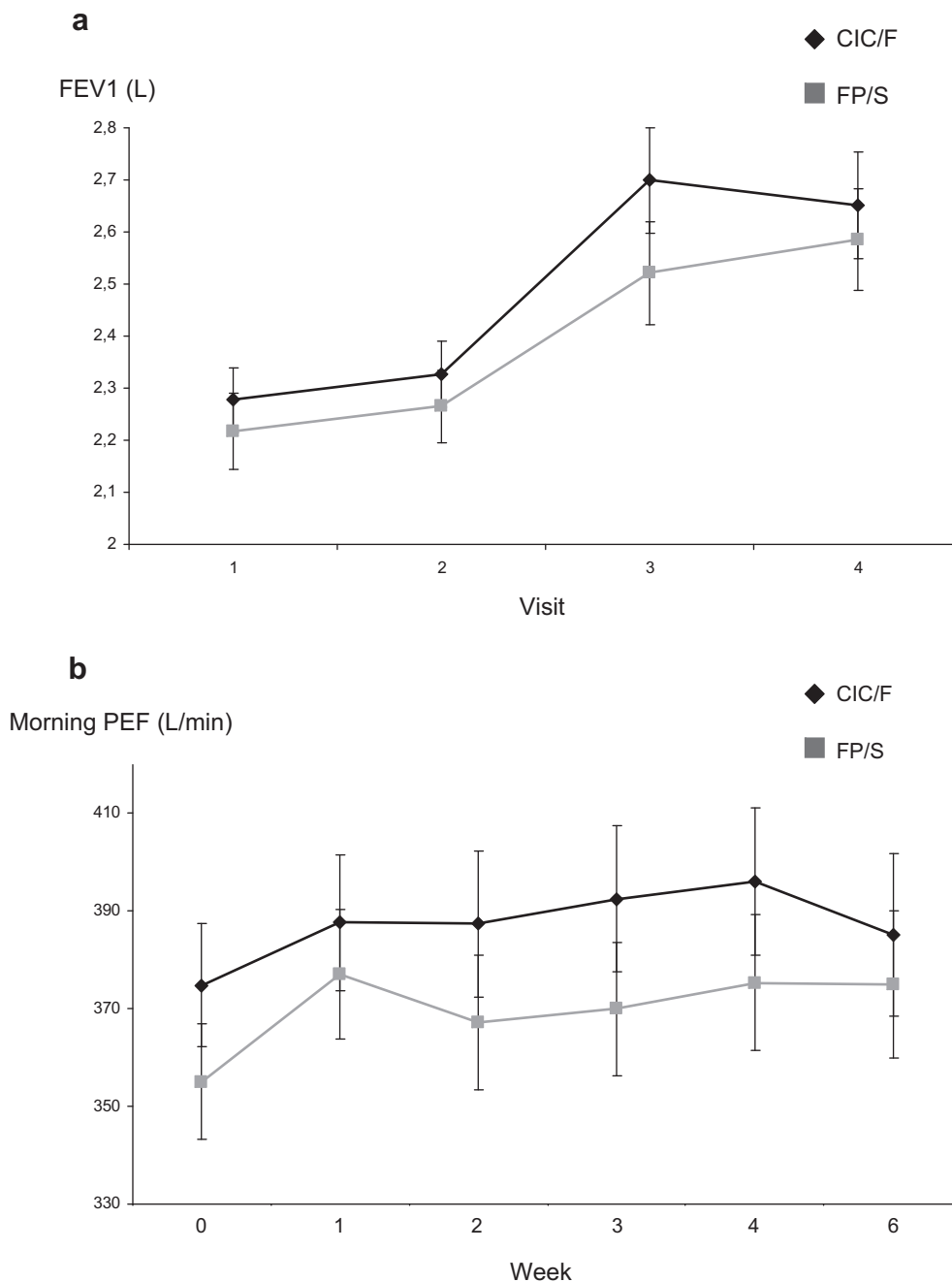

Figure 2 a) Time course of FEV1 (L) (PP analysis), Mean and SEM for the time course, PP. b) Time course of morning peak flow, Mean and SEM for the time course, PP.

parameters, either measured by patients twice daily or at the site visits, showed comparable increases in the two groups and are in line with previous study results.[20,21,30–32] In addition, comparable improvements in the two groups were observed in the assessment of clinical symptoms and in the use of rescue salbutamol, which significantly decreased from baseline to end of study with no difference between groups. The two combination treatments showed similar tolerability profiles.

Combination therapies are routinely used as part of regimens where the maintenance dose of ICS/LABA is titrated up to achieve stable asthma control, and, when adequate control is maintained, titrated down with the aim of minimizing the overall drug load whilst maintaining stable control.[19,33] Both patient compliance and long-term pulmonary function benefit from single inhaler treatment with LABA and ICS.[10,34,35] This treatment regimen allows the patient to perceive the relief of symptoms provided by the LABA, thus enhancing compliance, while receiving a maintenance dose of the ICS that acts on the chronic airways inflammation, hence improving disease control. Moreover, the use of fixed combinations reduces the direct and indirect treatment costs compared with the administration of the same drugs given by separate inhalers.[36] Taking into consideration the evidence-based advantages offered by the combined administration of LABA/ICS, the

Table 2 Change in FEV1 (L), FVC (L), FEF25-75% (L/s) from $T0$: within- and between-treatment differences, endpoint analysis (PP, mITT).

WITHIN

	N	Visit 2			Visit 4	Visit 4 − visit 2		
		Mean	% pred.	LSMean	LSMean	LSMean ± SE	95% CI	p-value[a]
FEV1								
PP analysis								
CIC640/F18	61	2.298	71.9	2.293	2.650	0.356 ± 0.045	0.267, 0.446	<0.0001
FP500/S100	62	2.289	72.3	2.293	2.582	0.288 ± 0.044	0.200, 0.376	<0.0001
mITT analysis								
CIC640/F18	81	2.376	72.5	2.323	2.643	0.320 ± 0.042	0.237, 0.402	<0.0001
FP500/S100	79	2.269	72.6	2.323	2.629	0.306 ± 0.042	0.223, 0.389	<0.0001
FVC								
PP analysis								
CIC640/F18	61	3.225	84.8	3.195	3.656	0.460 ± 0.060	0.341, 0.580	<0.0001
FP500/S100	62	3.166	83.1	3.195	3.479	0.284 ± 0.059	0.166, 0.401	<0.0001
mITT analysis								
CIC640/F18	81	3.367	85.9	3.283	3.681	0.398 ± 0.054	0.292, 0.505	<0.0001
FP500/S100	79	3.197	85.1	3.283	3.562	0.279 ± 0.054	0.172, 0.387	<0.0001
FEF25–75%								
PP analysis								
CIC640/F18	58	1.633	43.6	1.645	1.989	0.344 ± 0.071	0.204, 0.484	<0.0001
FP500/S100	61	1.656	45.0	1.645	2.072	0.427 ± 0.069	0.291, 0.563	<0.0001
mITT analysis								
CIC640/F18	78	1.672	44.0	1.642	1.941	0.299 ± 0.060	0.179, 0.418	<0.0001
FP500/S100	78	1.612	44.1	1.642	2.082	0.440 ± 0.060	0.321, 0.560	<0.0001

BETWEEN

	Test	Ref	n Test	Difference Test − Ref for visit 4 − visit 2				
				n Ref	LSMean±SE	95% CI	p-value non-inf.[b]	p-value sup.[c]
FEV1								
PP analysis	CIC640/F18	FP500/S100	61	62	0.068 ± 0.063	−0.057, 0.193	<0.0001	0.1412
mITT analysis	CIC640/F18	FP500/S100	81	79	0.013 ± 0.059	−0.103, 0.130	0.0002	0.4109
FVC								
PP analysis	CIC640/F18	FP500/S100	61	62	0.177 ± 0.084	0.010, 0.343	<0.0001	0.0190
mITT analysis	CIC640/F18	FP500/S100	81	79	0.119 ± 0.076	−0.032, 0.270	<0.0001	0.0602
FEF25–75%								
PP analysis	CIC640/F18	FP500/S100	58	61	−0.083 ± 0.098	−0.277, 0.111	NA	0.8011
mITT analysis	CIC640/F18	FP500/S100	78	78	−0.142 ± 0.085	−0.310, 0.026	NA	0.9510

CI = confidence interval, CIC640/F18 = ciclesonide/formoterol 320/9 μg twice daily, FP500/S100 = fluticasone propionate/salmeterol 250/50 μg twice daily, LS = least squares, SE = standard error of the LSMean
[a] Two-sided p-value for within-treatment differences, significance level 5%.
[b] One-sided p-value for non-inferiority, significance level 2.5%, non-inferiority margin = −200 mL.
[c] One-sided p-value for superiority, significance level 2.5%.

studied ciclesonide/formoterol combination is a valid alternative in the treatment of asthma. Moreover, in view of the fact that ciclesonide is an established ICS used worldwide, the availability of a ciclesonide/formoterol combination may also allow patients not adequately controlled with ICS alone to increase treatment intensity using a familiar molecule in the same inhaler. In addition, due to its pharmacodynamic properties formoterol, a full β2-agonist is thought to be more efficacious than the partial β2-agonist salmeterol, in particular during periods of increased inflammation or challenge.[12] Although not tested in the present trial, the specific properties of formoterol, among them its rapid onset of action and the clear dose-response-relationship, offer the potential of using ciclesonide/formoterol as maintenance and reliever therapy, which simplifies treatment for both patients and clinicians by delivering effective asthma control using a single inhaler. This enables patients to respond at the first sign of symptoms by taking additional as-needed inhalations of ciclesonide/formoterol to achieve rapid und sustained relief of symptoms, with every dose being accompanied by additional anti-inflammatory therapy.[37] Another attractive aspect of the fixed ciclesonide/formoterol combination is the 24 h duration of action of both components, offering patients the flexibility to use the drug on a once daily basis either in the morning or in the evening.[22,38]

LABAs are the first choice add-on treatments for patients poorly controlled on low-dose ICS, with a SABA to be provided as reliever medication.[5] However, overuse of SABAs or formoterol, a rapid- and long-acting β-agonist, as reliever medication is a well known problem for asthma patients,[39,40] and it has long been established that increased reliever use, without sufficient anti-inflammatory therapy, increases the risk of asthma morbidity and mortality.[41,42] In fact, overuse of SABA or LABA without concomitant ICS should be avoided as it could lead to under-treatment of the inflammatory process, masking inflammation, and so leading to more severe and potentially life-threatening exacerbations.[41] Recently the safety of LABA treatment in patients with asthma has been questioned.[43,44] The United States Food and Drugs Administration (FDA) mandated label changes impacting LABA use in the USA,[45] and requested new studies of their efficacy and safety. The FDA has determined single-ingredient LABAs should only be used in combination with an asthma controller medication and should only be used long-term in patients whose asthma cannot be adequately controlled on asthma controller medications.[46] Ciclesonide/formoterol treatment ensures anti-inflammatory therapy is delivered in combination with a LABA and thus appears as a regimen that may also contribute to the safety of combination therapy. More so, using a single ICS/LABA inhaler both for maintenance and reliever therapy is the only therapeutic strategy in asthma which definitely prevents SABA or LABA monotherapy.[19,35]

The present study has several limitations. Firstly, daily doses of 640 μg ciclesonide, and 500 μg fluticasone were tested. Based on the most recent GINA guidelines,[5] the ciclesonide dose seems to be more potent than the fluticasone dose. However, the GINA equivalence table is solely based on studies with the commercially available ciclesonide preparation, a solution delivered by a HFA MDI. HFA MDIs generate a greater mass of fine particles and yield a finer spray of particles, resulting in a better pulmonary deposition and greater percentage of the inhaled dose being deposited in the small airways.[22] In contrast, in the present study a newly developed powder formulation of ciclesonide/formoterol was used. Appropriate dosing of this new compound was estimated on the basis of phase I safety

Table 3 Percent days without symptoms and use rescue medication n: within- and between-treatment differences, per/post comparison (mITT, PP).

WITHIN

	N	I_{run-in} Median	$I_{last/end}$ Median	$I_{last/end} - I_{run-in}$		
				HL point estimate	95% CI	p-value[a]
PP analysis						
CIC640/F18	64	41.7	73.0	27.0	20.2, 33.9	<0.0001
FP500/S100	68	38.5	74.0	22.8	15.9, 29.8	<0.0001
mITT analysis						
CIC640/F18	81	41.7	75.0	25.3	19.2, 31.4	<0.0001
FP500/S100	79	30.8	66.7	20.5	14.5, 27.5	<0.0001

BETWEEN

	Test	Ref	n Test	n Ref	Difference Test − Ref for $I_{last/end} - I_{run-in}$			
					HL point estimate	95% CI	p-value 2-sided[b]	p-value sup.[c]
PP analysis	CIC640/F18	FP500/S100	64	68	4.0	−6.0, 13.8	0.4163	0.2082
mITT analysis	CIC640/F18	FP500/S100	81	79	4.7	−4.6, 13.4	0.3002	0.1501

CI = confidence interval, CIC640/F18 = ciclesonide/formoterol 320/9 μg twice daily, FP500/S100 = fluticasone propionate/salmeterol 250/50 μg twice daily, HL = Hodges-Lehmann, I_{run-in} = run-in interval (two weeks before $I0$), $I_{last/end}$ = interval of the last four treatment weeks (mITT/PP analysis).
a   Two-sided p-value for within-treatment differences, significance level 5%.
b   Two-sided p-value for between-treatment differences, significance level 5%.
c   One-sided p-value for superiority, significance level 2.5%.

data and of the fine particle fraction of the powder formulation which is smaller than that of the ciclesonide HFA MDI. The results of the trial support the assumption that the doses of the two corticosteroids and of the two β-agonists are more or less equivalent. However, it cannot be ruled out that the minor differences in effects of the two compounds were partly due to non-equivalent corticosteroid doses. This is true even though local and systemic tolerability were similar. Secondly, CIC/F patients were younger, and the median duration of asthma was longer in the FP/S patients, unusually for a randomized trial. It cannot be excluded that this disparity had an influence on the outcome of the trial. Finally, a treatment period of some six weeks is definitely too short to address patient-relevant endpoints such as exacerbations, and the small number of patients together with the short duration of the trial makes it impossible to detect rare adverse events. This is true despite the fact that both ciclesonide and formoterol are widely used as single agents for many years, and that it is highly unlikely that the same drugs given as a fixed combination will behave differently from a free combination of the same drugs. Further studies will have to address these issues as well as the question if the results seen in this study can be generalized to patients with other degrees of severity. Similarly, no difference was found in the rates of asthma exacerbations. However, it was not possible to treat exacerbation rate as a primary endpoint in the present study, since exposure time was limited and more patients are needed in order to detect potential differences between treatments.

Conclusion

The present study is the first to evaluate the efficacy and safety of a DPI containing the combination ciclesonide/formoterol together with a standard combination of fluticasone/salmeterol in patients with moderate asthma. Non-inferiority of CIC/F to FP/S treatment was demonstrated regarding the primary variable FEV1 and no difference between treatments was observed for the co-primary variable patient perceived asthma control (based on symptoms and use of rescue medication). Both treatments were effective in improving lung function and all secondary efficacy variables in asthma. The 6-week treatment with CIC/F did not indicate any new safety risks of both components in this patient group. The new ciclesonide/formoterol combination is a valid alternative for the treatment of asthma patients not controlled on an ICS alone. It has an efficacy and safety profile comparable to the fixed budesonide/formoterol and beclomethasone/formoterol combinations.[20,21,30–32,47–49]

Funding

Authors contributions

SK made substantial contributions to the interpretation of data and drafted the manuscript. RB participated in the design of the study, made substantial contributions to analysis and interpretation of data, was involved in drafting the manuscript and in revising it critically for important intellectual content.

All authors read and approved the final manuscript.

Competing interests

SK served as an advisor to GlaxoSmithKline and received lecture fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Nycomed, and Talecris.

RB reports having served as a consultant to Altana Pharma, AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, Novartis, Roche and Pfizer; having been paid lecture fees by Altana Pharma, AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, Novartis, Roche and Pfizer, having received grant support from Altana Pharma, AstraZeneca, Boehringer Ingelheim, Schering Plough, Chiesi Farmaceutici, GlaxoSmithKline, Pfizer.

Acknowledgements

Supplementary material

Supplementary data related to this article can be found online at doi:10.1016/j.rmed.2011.08.010.

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