Assessment of Efficacy and Safety between Two Formulations of Formoterol Fumarate in Adolescents and Adults with Persistent Asthma

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Abstract

Objective: The mandatory replacement of chlorofluorocarbons (CFCs) in pressurized metered dose inhalers (pMDIs) with non ozone depleting propellants such as hydrofluoroalkanes (HFA 134a) requires clinical testing that ensures the reformulated aerosol with HFA is as effective and well tolerated as the original CFC version. In view of this, a multicentre, randomised, parallel-group, double-blind study was conducted to compare the safety and efficacy of formoterol fumarate delivered by a MDI using the hydrofluoroalkane (HFA) 134a propellant (Cipla Ltd) with the CFC formulation (Foradil CFC pMDI, Novartis, UK) in adolescents and adults.

Methods: Patients on a stable dose of inhaled corticosteroids with a scope for improvement based on mean morning peak expiratory flow (PEF) and symptoms were randomised to receive formoterol HFA MDI 24 mg twice daily or formoterol CFC MDI 24 mg twice daily for 12 weeks. The primary efficacy variable was the mean morning PEF and secondary variables included FEV1, symptom scores, use of relief medication and safety assessments.

Results: The difference between the treatments in the adjusted mean morning PEF (formoterol HFA–formoterol CFC) was -4.68 L/min (95% CI: -13.45, 4.09). The lower limit of the 95% confidence interval was within the pre-defined limit (20 L/min) set for non-inferiority. The results of the secondary endpoints supported the findings of the primary endpoint. The incidences of adverse events (AEs) were similar for both formulations.

Conclusion: The results of this study confirm that formoterol HFA pMDI is as effective as formoterol CFC pMDI in adolescents and adults.

Introduction

Although metered dose inhalers (MDIs) were introduced >50 years ago, they still remain the most popular and widely used inhalation devices in the treatment of lung disease, with ~340 million units used worldwide each year [1,2]. Although the newer dry powder inhalers offer advantages for some patients in terms of the coordination of actuation with inhalation [3], MDIs are economical to manufacture, convenient to use, and popular with patients.

For many years, chlorofluorocarbons (CFCs) have been used as medicinal aerosol propellants and solvents in MDIs owing to their non-toxic, inert and non-flammable properties. However, in accordance with the Montreal Protocol 1987 [4], which stipulates the phasing out of compounds that deplete ozone, endeavours have been made by the pharmaceutical industry to replace all CFC inhalers with alternatives, such as hydrofluoroalkanes (HFAs).

Formoterol delivered via CFC MDI is a safe and effective, long-acting beta2-agonist indicated for the treatment of asthma. It has a duration of action of >12 hours and protects against bronchoconstriction induced by challenge with histamine, methacholine, and exercise [5,6]. Any reformulation of the CFC MDI for formoterol would have to have equivalent therapeutic properties.

A CFC-free MDI formulation of formoterol has been developed by Cipla Ltd, India, which uses 1,1,1,2-tetrafluoroethane , an HFA propellant more commonly referred to as HFA-134a.

The objective of the present research programme was to compare the safety and efficacy of formoterol reformulated in HFA-propellant with the existing formoterol CFC MDI (Foradil, Novartis) at equal doses.

Methods

Patient selection

Male or female patients aged 12 years or older with a confirmed diagnosis of asthma [as defined by GINA guidelines] and a history of using inhaled corticosteroid (ICS) (either beclometasone or budesonide (≤1000 µg/day) or fluticasone (≤500 µg/day)) for at least 4 weeks before the screening visit were included. Patients were required to have a forced expiratory volume in one second (FEV_1) ≥50% and ≤85% of the predicted normal value when not taking short-acting bronchodilator medication, and were able to demonstrate a ≥15% improvement in FEV_1 within 15-30 minutes after inhalation of salbutamol (400 µg) unless reversibility had been documented in the previous 6 months.

All subjects were able to use the peak flow meter, to perform the required pulmonary function tests, and demonstrated correct use of the pMDI. Subjects were excluded from the study if they had received oral, depot or parenteral corticosteroids within 1 month of screening, or long acting bronchodilators (LABAs) or slow release bronchodilators within 2 weeks of screening. Subjects were also excluded if they had any clinically relevant condition that might compromise the safety of the subject or that in itself, or by its treatment, might interfere with

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the efficacy results of the study; or had a smoking history of ≥10 pack years. All women enrolled had negative pregnancy tests, and those of childbearing potential practiced acceptable methods of birth control. All subjects gave written, informed consent and were, in the opinion of the investigator, able to comply with the requirements of the protocol.

Study design

This was a randomised, double blind, multicentric, parallel-group study with a run-in period of 2-weeks, a treatment period of 12-weeks, followed by a switch-over evaluation period of 2-weeks.

Ethics committee approval was obtained from each participating centre and the study was conducted in accordance with good clinical practice guidelines and the Declaration of Helsinki, 1996.

Eligible subjects were enrolled into the study and entered the run-in period during which they continued to take their prescribed inhaled corticosteroid (ICS) treatment. LABAs were not permitted but the short-acting β_2-agonist, salbutamol, was permitted as rescue medication. Subjects who were symptomatic at the end of the run-in period were then randomised to a 12-week treatment phase to either formoterol-HFA pMDI (test product) or formoterol-CFC pMDI (comparator) in a 1:1 ratio and were instructed to take 2 puffs (24 mcg) twice daily in the morning and in the evening approximately 12 hours apart during the 12 week treatment period. Since the test and comparator product devices differed in appearance, subjects also received the appropriate placebo pMDI. Subjects were followed up at 1, 3, 6, 9 and 12 weeks after randomisation to assess safety and efficacy.

Daily record cards were completed throughout the run–in and treatment periods. Prior to use of rescue or study medication, patients were instructed to perform three PEF measurements and record the highest value in the daily diary each morning on rising and each evening before going to bed. PEF was measured with a Mini- Wright peak flow meter (Clement Clark International Ltd, Harlow, UK). At all clinic visits, forced expiratory volume in 1 second (FEV$_1$) was measured using spirometry.

Each day, in addition to morning and evening PEF, the patients also recorded the number of occasions that relief medication was used during the previous day and night, and the asthma symptom scores. A patient's assessment of asthma symptoms during the day was recorded using a 0-4 rating scale, while nighttime symptom scores were rated on a 0-3 scale, where ratings of 3 and 4 indicated very severe symptoms on the respective scales.

At the end of the run-in period, patients with scope of improvement were eligible to enter the treatment period if they fulfilled 2 of the following criteria:

• Daytime asthma score >2 on at least 3 of the last 7 days of the run-in period.

• Required salbutamol>twice daily on at least 2 days of the last 7 days of the run-in period.

• Nocturnal awakenings due to asthma on at least 2 days of the last 7 days of the run-in period.

• Diurnal PEF variation >20% on at least 2 days.

Patients who experienced an exacerbation of their asthma during the run-in period were excluded from the study.

At the end of the 12-week treatment period, subjects who received formoterol-CFC during the treatment period were re-randomised (1:1) to receive either formoterol-HFA or to continue with formoterol-CFC to evaluate further the effects of switching from CFC to HFA. Subjects who received formoterol-HFA during the treatment period continued for another 2 weeks on formoterol-HFA.

Safety was assessed by recording of all adverse events (AEs) and serious adverse events (SAEs) and assessing changes after treatment initiation for ECG, tremor, vital signs, serum potassium and glucose levels, and clinically significant laboratory changes from end of treatment period compared with baseline values.

Statistical Analysis

The primary efficacy variable was the adjusted mean change in morning pre-dose PEF over the 12-week treatment period.

Assuming a variability for mean morning PEF of 60 L/min, a non-inferiority limit of 15 L/min, a 5% significance level, 80% power and a two-sided t-test, it was estimated that the number of patients required in the per-protocol (PP) population to demonstrate non-inferiority was 115 per treatment group. To accommodate for a 20% exclusion rate from the ITT population, 138 patients were planned to be randomised per treatment group. Both the ITT and PP populations were used for analysis of the primary efficacy endpoint.

The primary efficacy variable was analysed by analysis of covariance (ANCOVA) with the baseline value prior to treatment initiation (measured as the mean of the daily values over the last seven days of the two-week run-in period), and centre as covariates.

The treatment comparison was assessed by constructing, based on ANCOVA, a two sided 95% confidence interval (CI) for the difference between the two treatment groups (CFC as 'control' and HFA as 'test' product 'HFA-CFC'). If the lower bound of the 95% CI was greater than −20 L/min, it could be concluded that HFA was not inferior to CFC. Non inferiority was assessed based on the primary efficacy variable evaluation only.

The secondary efficacy variable FEV$_1$ was analysed using ANCOVA with baseline and centre as covariates while for other secondary efficacy variables, the differences in the two treatment groups for total symptom scores, intake of rescue medication were tested by nonparametric tests. AEs, SAEs and discontinuations due to AEs were reported descriptively. All other safety data was collated and summarised by treatment group.

Results

Three hundred and twenty four patients were recruited into the study. Of these, 44 patients were withdrawn prior to randomisation. The most common reasons for withdrawal were patients not fulfilling entry criteria (n=18) or not fulfilling the randomization criteria (n=26).

Of the 280 subjects who were randomised and received at least one dose of the study medication (HFA group n= 141, CFC group n=139), 2 subjects were withdrawn (lost to follow-up) after randomization in the HFA group and 1 subject in the CFC group. Therefore, 277 subjects were included in the ITT population (139 subjects in the HFA group and 138 subjects in the CFC group). Of the 277 subjects in the ITT population, 33 subjects were excluded from the PP population (Table 1).

Demography and baseline characteristics were well matched between the two treatment groups (Table 2). Both the treatment groups had populations with comparable baseline lung function (PEF, percentage predicted FEV$_1$ and FEV$_1$). The mean % predicted FEV$_1$ was approximately

68% and 66% in HFA and CFC groups respectively. At baseline,

	Formoterol HFA	Formoterol CFC
Randomised	141	139
Withdrawn immediately after randomization (lost to follow up)	2	1
Included in ITT population	139	138
Completed	123	129
Included in PP population	120	124
Excluded from PP population	19	14
Major protocol violations	7	7
Adverse events	2	2
Lost to follow up	9	5
Withdrawal of consent	1	0

Table 1: Patient disposition.

	Formoterol HFA	Formoterol CFC
Sex, Males/Females	73/66	62/76
Age, years		
Mean	38.2	39.1
Range	15.2-64.3	12.1-65.8
FEV_1 (L) Mean(SD)	1.87 (0.54)	1.74 (0.52)
FEV_1 (% predicted) Mean(SD)	68.1 (11.9)	66.1 (13.3)
PEF (L/min) Mean (SD)		
Morning	270 (82.8)	259 (72.9)
Evening	267 (83.0)	257 (75.2)
Salbutamol use, puffs/night (Median)	1.56	1.54
Salbutamol use, puffs/day (Median)	1.95	1.73
% of daytime asthma scores=0 *	27.3	27.1
% of nighttime asthma scores=0**	29.5	30.2

*Unless otherwise expressed, values presented as means (SD); * 0=very well, no symptoms; **0=no symptoms, slept through the night

Table 2: Characteristics and asthma profile of efficacy population at baseline.

both treatment groups showed similar baseline symptom scores and use of relief medication.

Mean morning PEF

Mean morning PEF values derived from diary card readings were analysed for both PP and ITT populations. In both the populations, a clinically relevant increase in mean morning PEF at week 12 was observed in both formoterol HFA and formoterol CFC treatment groups (Figure 1).

In the ITT population, the overall improvement in mean morning PEF, adjusting for centre and baseline was 26.3 and 21.6 L/min in the formoterol HFA and formoterol CFC groups, respectively (Table 3). The estimated treatment difference (formoterol HFA–formoterol CFC) was -4.68 L/min and the 95% confidence interval was (-13.45, 4.09). The lower CI limit was within the pre-defined non-inferiority limit of 20 L/min, indicating that the HFA formulation is at least as effective as the CFC formulation.

For the PP population, the 95% confidence interval was -12.93, 4.94 which further confirmed noninferiority of the HFA formulation.

Clinic FEV1

No significant difference in clinic FEV_1 at endpoint was observed between formoterol HFA and formoterol CFC in both the ITT and PP populations (Table 4). However, the mean FEV_1 at baseline in the ITT population was slightly higher in the HFA group (1.87 L) compared

with the CFC group (1.74 L). The difference was not statistically significant at baseline or at Week 1. However, at Weeks 3, 6, 9 and 12, the mean FEV_1 was statistically significantly higher (p<0.05) in the HFA group compared with the CFC group.

Symptom scores and use of relief medication

Median daytime and nighttime symptom scores as well as daily use of relief medication were reduced by both formulations (Figure 2 and Table 5).

Switch-evaluation data

Following a further two weeks treatment, the morning PEF, evening PEF and diurnal variation were comparable between treatments indicating no deterioration in respiratory parameters after switching from CFC to HFA.

Safety

Overall, both treatment formulations were well tolerated and had comparable AE profiles (Table 6).

The incidence of AEs was similar in the two groups. The most common AEs during the treatment period were headache followed by pyrexia. Four SAEs occurred during the study, 2 SAEs in each treatment group, none of which was related to study medication. No clinically significant changes from baseline were found in vital-sign measurements, ECG, tremor assessment or laboratory tests in either group throughout the study.

Conclusions

For the primary efficacy variable (morning PEF) as the two sided 95% CI for the difference between the two treatment groups lies well above the proposed non-inferiority limit of –20 L/min, it can be concluded that the formoterol-HFA pMDI is clinically non-inferior to the formoterol-CFC pMDI. This conclusion is supported by the secondary efficacy variables. There was no reduction in morning or evening PEF after a two week switch from CFC to HFA. The nature and frequency of AEs in both groups were similar.

Discussion

This study suggests that substantial clinical efficacy may be achieved with formoterol at a dose of 24 mcg twice daily when administered via an MDI using either a CFC or HFA propellant. Furthermore, the magnitude of the clinical improvement from baseline observed with
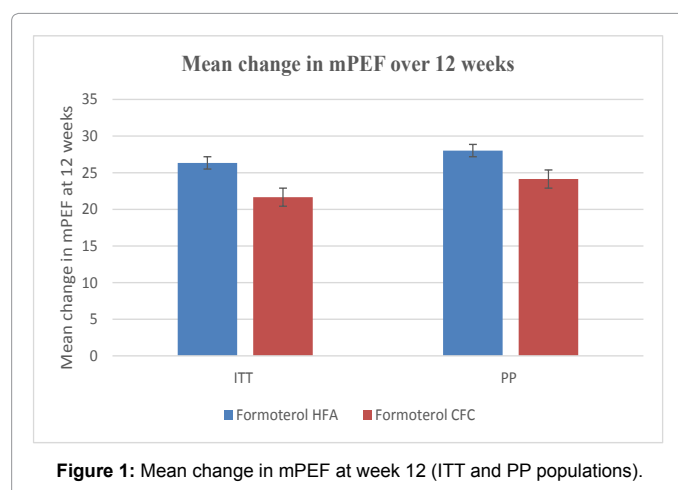

Figure 1: Mean change in mPEF at week 12 (ITT and PP populations).

Lung function parameter	Treatment	N	Mean (SD) morning PEF during treatment	Adjusted mean change from baseline	Mean difference (HFA vs. CFC) (95% CI)
mPEF (L/min)-ITT	Formoterol HFA	139	295 (84.4)	26.34	-4.68 (-13.45; 4.09)
	Formoterol CFC	138	281 (73.1)	21.66	
mPEF (L/min)-PP	Formoterol HFA	120	301 (84.5)	28.02	-3.99 (-12.93; 4.94)
	Formoterol CFC	124	286 (69.3)	24.14	

Table 3: Statistical analyses of mPEF for formoterol HFA pMDI versus formoterol CFC pMDI.

FEV$_1$ (L) Mean (SD)	Formoterol HFA N=138	Formoterol CFC N=138
Week 1	1.89 (0.57)	1.75 (0.54)
Week 3*	1.92 (0.60)	1.79 (0.52)
Week 6*	1.90 (0.61)	1.77 (0.51)
Week 9*	1.93 (0.59)	1.78 (0.51)
Week 12*	1.87 (0.61)	1.75 (0.53)

*p<0.05 formoterol HFA versus formoterol CFC

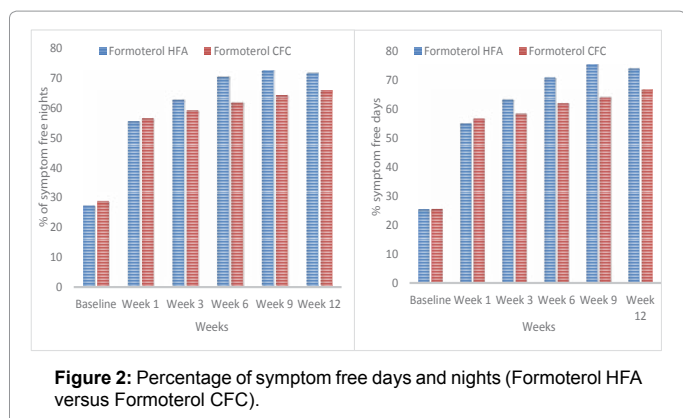**Table 4:** Mean FEV1 over 12 weeks (Formoterol HFA versus Formoterol CFC).

Figure 2: Percentage of symptom free days and nights (Formoterol HFA versus Formoterol CFC).

	Formoterol HFA	Formoterol CFC
Nighttime use of rescue		
Baseline	1.56	1.54
12 weeks	0.10	0.19
Daytime use of rescue		
Baseline	1.95	1.73
12 weeks	0.05	0.15

Table 5: Mean number of puffs of rescue medication usage at baseline and at 12 weeks.

	Formoterol HFA	Formoterol CFC
Pyrexia	13(1.42)	30 (3.60)
Rhinitis	17 (4.96)	17 (3.60)
Rhinitis Allergic	13 (2.13)	18 (2.16)
Headache	29 (7.80)	25 (9.35)

Table 6: Frequency (%) of most commonly reported (>2%) adverse events.

both treatments was therapeutically similar, as evidenced by statistical non-inferiority of the primary efficacy parameter assessed.

The change in mean morning PEF, was deemed clinically meaningful. Furthermore, no statistically significant differences between the two formulations were observed in mean morning PEF, in either population, as the lower limits of the 95% confidence intervals were above the pre-defined 20 L/min non-inferiority limit. These results indicate comparable efficacy between the HFA and CFC formulations of formoterol.

Marked improvements from baseline in FEV$_1$, daytime and nighttime symptom scores and daily use of relief medication were observed with both treatments, further illustrating the efficacy of formoterol in the treatment of asthma.

The baseline and eligibility characteristics of the population under study showed that there was room for clinical improvement of lung function and asthma symptoms in response to study medication, hence avoiding a conclusion of non inferiority through nonresponse.

Additionally, the observed mean improvements in the clinical parameters evaluated for the primary endpoint mPEF were consistent between the ITT and PP populations, thereby confirming the validity of the study results. The two formulations of formoterol were well tolerated and demonstrated comparable tolerability profiles, with the formulations exerting similar incidences of AEs, which were not unexpected for the populations under investigation.

The operation of a MDI is independent of a patient's diagnosis, and

the pharmacological mechanism of formoterol is the same for asthma and COPD. While comparable efficacy of the HFA formulation and the CFC formulation of formoterol was demonstrated in asthmatic populations in this study, there is no reason to anticipate that the effects of the formoterol HFA inhaler will differ from those of the CFC inhaler in terms of bronchodilator efficacy in patients with COPD. This is because other drug classes, redeveloped from CFC- to HFA-containing inhalers, have shown similar clinical benefits in COPD.

The comparable efficacy and tolerability profiles of the formoterol HFA and formoterol CFC formulations, therefore, facilitate a seamless transition to the new CFC-free inhalers.

In summary, this study has shown that in adolescents and adults with persistent asthma may be switched from the formoterol CFC MDI (Foradil) to the formoterol HFA MDI (Cipla Ltd) with maintenance of good clinical efficacy and tolerability profiles.

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