Respiratory Medicine (2013) 107, 1330–1338

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.elsevier.com/locate/rmed

Fluticasone/formoterol dry powder versus budesonide/formoterol in adults and adolescents with uncontrolled or partly controlled asthma☆

A. Cukier [a], C.M.A. Jacob [b], N.A. Rosario Filho [c], J. Fiterman [d], E.O. Vianna [e], J.L. Hetzel [f], M.A. Neis [g], E. Fiss [h], F.F.M. Castro [i], A.L.G. Fernandes [j], R. Stirbulov [k], E. Pizzichini [l,*], AIR Brazilian Study Group

[a] *Pulmonary Division, Heart Institute (InCor), Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Av. Dr. Eneas de Carvalho Aguiar, 44 — bloco I — 1° andar, São Paulo, SP 05403-000, Brazil*

[b] *Department of Pediatrics, State University of São Paulo, Av. Dr. Eneas Carvalho de Aguiar, 647, P1/P2, São Paulo, SP 05403-000, Brazil*

[c] *Departamento of Pediatrics, Federal University of Paraná, Rua Padre Camargo, 530 — 1° andar, Curitiba, PR 80060-240, Brazil*

[d] *Pontifical Catholic University of Rio Grande do Sul — São Lucas Hospital, Av. Ipiranga, 6990 — 4° andar — centro de pesquisa clinica, Porto Alegre, RS 90610-000, Brazil*

[e] *Medical School of Ribeirão Preto, University of S. Paulo, Avenida Bandeirantes, 3900, Ribeirão Preto, SP 14049-900, Brazil*

[f] *Santa Casa de Misericordia de Porto Alegre, Av. Independência, 75 — Pavilhão Pereira Filho — 1° andar, Porto Alegre, RS 90035-074, Brazil*

[g] *Centro Paulista de Investigação Clínica, Rua Moreira e Costa, 342 — Ipiranga, São Paulo, SP 04266-010, Brazil*

[h] *Faculdade de Medicina ABC, Avenida Principe de Gales, 821, Santo André, SP 09061650, Brazil*

[i] *Instituto de Pesquisa Clínica Medicina Avançada, Praça Américo Jacomino, 55, Vila Madalena, São Paulo, SP 05437-000, Brazil*

[j] *Federal University of São Paulo, Rua Botucatu, 740 — 3° andar — Vila Clementino, São Paulo, SP 04062-023, Brazil*

☆ Conducted by Asthma Inhaled Research (AIR): comparing fluticasone propionate combined with formoterol versus Symbicort® — AIR Brazilian Study Group.[1]

* Corresponding author. Tel.: +55 48 3234 7711, +55 48 9971 8273 (mobile).
E-mail addresses: pizzichi@matrix.com.br, emiliopizzichini@me.com (E. Pizzichini).

[1] AIR Brazilian Study Group members include: Ana Carla S. Araujo, Anna Beatriz Naumes, Andrea Gimenez, Antonio Carlos Pastorino, Carlos Toufen Junior, Claudia Loss Reck, Clóvis Eduardo Santos Galvão, Daniela Cavalet Blanco, Debora Carla Chong e Silva, Denise A. Padilha Kroth, Fabiane Kahan, Fernanda Spilimbergo, Herberto José Chong Neto, José Roberto Jardim, Lilian Ballina Caetano, Manuela Cavalcanti, Marcia M.M. Pizzichini, Leila Marques Steidle, Rodrigo Athanazio, Samia Rached, Samir Drocoulaks, Sonia Maria Foresin, Suzana Zelmanovitz, Valéria Cristina V. Martins.

0954-6111/$ - see front matter
http://dx.doi.org/10.1016/j.rmed.2013.06.018

[k] *Santa Casa School of Medical Sciences in São Paulo, Rua Dr. Cesário Mota Junior, 112 — UPCOR — sala 1, São Paulo, SP 01221-900, Brazil*
[l] *Federal University of Santa Catarina, Campus Universitário — Trindade, Florianópolis, SC 88040-970, Brazil*

Received 22 March 2013; accepted 23 June 2013
Available online 9 July 2013

KEYWORDS
Asthma control questionnaire;
Clinical trial;
Forced expiratory volume in 1 s;
Single inhaler;
Non-inferiority;
Morning peak expiratory flow

Summary
This 12-week study compared the efficacy and safety of a fixed combination of fluticasone propionate plus formoterol (FL/F) 250/12 μg b.i.d. administered *via* a dry powder inhaler (DPI) (Libbs Farmacêutica, Brazil) to a combination of budesonide plus formoterol (BD/F) 400/12 μg b.i.d. After a 2-week run-in period (in which all patients were treated exclusively with budesonide plus formoterol), patients aged 12—65 years of age ($N = 196$) with uncontrolled asthma were randomized into an actively-controlled, open-labeled, parallel-group, multicentre, phase III study. The primary objective was to demonstrate non-inferiority, measured by morning peak expiratory flow (mPEF).

The non-inferiority was demonstrated. A statistically significant improvement from baseline was observed in both groups in terms of lung function, asthma control, and the use of rescue medication. FL/F demonstrated a statistical superiority to BD/F in terms of lung function (FEV_1) ($p = 0.01$) and for asthma control ($p = 0.02$). Non-significant between-group differences were observed with regards to exacerbation rates and adverse events.

In uncontrolled or partly controlled asthma patients, the use of a combination of fluticasone propionate plus formoterol *via* DPI for 12-weeks was non-inferior and showed improvements in FEV_1 and asthma control when compared to a combination of budesonide plus formoterol. (Clinical Trial number: ISRCTN60408425).

Introduction

Asthma is a worldwide disease associated with a growing burden in terms of morbidity, lower quality of life, and healthcare costs [1]. The goal of therapy in asthma is to achieve and maintain clinical control by reducing the patient's exposure to factors that exacerbate asthma and by using medications for the purposes of relief and control. For patients with uncontrolled asthma treated with inhaled corticosteroids (ICS) alone, international guidelines recommend a combination of inhaled corticosteroids (ICS) and long-acting β2-agonists (LABA) [1]. The use of an ICS/LABA combination in 1 inhaler may be more effective due to convenience and ease of use by improving patient compliance and long-term control [2,3].

Fluticasone propionate is an inhaled corticosteroid with high potency in vitro [4], high topical anti-inflammatory activity [5], and a rapidly induced protective effect [6]. Fluticasone propionate has been shown to be effective in adults and children with regards to treating chronic asthma [7]. Formoterol is a LABA with a very quick onset of action [8]. It has been used as a maintenance therapy and as a relief medication in combination with an ICS [9].

The FL/F combination in a single, pressurized, metered dose inhaler has been compared with the single agent treatment of either propionate fluticasone or formoterol and with combination of either fluticasone/salmeterol or budesonide/formoterol which to the majority concluded similar efficacy and safety [10—17]. In patients with severe asthma, the combination of FL/F showed similar efficacy and similar patient tolerance [10] as compared to single agents. In patients with mild-to-moderate asthma, the FL/F combination showed superior efficacy compared to either single agent fluticasone, formoterol, or placebo [13]. FL/F in a single aerosol inhaler was also compared with fluticasone propionate plus salmeterol, resulting in similar efficacy and a faster onset of action [11]. FL/F was also compared with budesonide plus formoterol and, again, showed comparable efficacy [12].

Chronic asthma control remains suboptimal despite the continued development of improved treatments for asthma, particularly in Latin America [18,19]. The consequences of suboptimal asthma control include a poor quality of life, frequent and urgent health care visits, an increase in the risk of asthma exacerbations, and increased mortality [20]. Alternative treatment options, with different combinations and formulations, may provide more flexibility with regards to adjusting to a patient's clinical severity and device preferences. This flexibility in treatment has the potential to increase compliance and effectiveness of therapy [21,22]. The rationale behind combining fluticasone propionate and formoterol (FL/F) is to provide the benefits of a high-potency anti-inflammatory agent with the fast onset of action of a β-2 agonist in a new formulation (dry powder) using a single inhaler.

Previous studies using metered dose inhaler showed similar efficacy between FL/F and others combinations. This is the first study to evaluate the fixed combination of

FL/F administered *via* a dry powder inhaler. It was designed in order to demonstrate the non-inferiority of the fixed combination of FL/F in comparison with the fixed combination of budesonide/formoterol (BUD/F) in the treatment of uncontrolled and partly controlled asthma patients. The BUD/F combination was selected for comparison because it contains the same LABA, *i.e.* formoterol.

Material and methods

Study design

This randomized, open, parallel-group study was conducted over 12 weeks (with an additional 2-week run-in period) in 11 research centers in Brazil (Clinical Trial number: ISRCTN60408425). The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice, and approved by an independent ethics committee on human research at each institution. All patients were provided with written informed consent. The study was conducted from August 2010 to March 2011.

The patients who qualified for the study based on the inclusion and exclusion criteria (as described below) started a 2-week run-in period in which all patients were treated with budesonide plus formoterol (Symbicort® Turbohaler®) at a dose of 400/12 μg twice daily. At the same time, they received PIKO-1 peak flow meters, rescue medication (salbutamol), and diaries for data collection. All other asthma medication was discontinued. Patients who had satisfactory compliance (<8 missed doses during the run-in period), had a predicted a post-bronchodilator FEV_1 of >60%, and had uncontrolled or partially controlled asthma, were randomized to receive the same dose of budesonide plus formoterol used in the run-in period or 250 μg of fluticasone propionate plus 12 μg formoterol twice daily (Duonare®, Libbs Farmacêutica, Brazil). The daily dose of 500 μg of propionate fluticasone used in this study is equivalent of 800 μg of budesonide [1]. Lung function assessments, reviews of patient's diaries and safety records were evaluated at weeks 4, 8 and 12. At each visit, patients completed a lung function test before receiving their morning dose.

Study patients

Males and females aged between 12 and 65 years, with a diagnosis of asthma for ≥3 months prior to screening, a body mass index between 19 and 30 kg/m^2, and currently receiving treatment with a combination therapy of a LABA and an ICS (800 μg budesonide or equivalent) for ≥30 days were included in the study. Patients were required to have partially controlled (patients with at least one of the following characteristic: daytime symptoms twice/week; need for reliever treatment twice/week; any limitation of activities; any nocturnal symptoms; or lung function less than 80% of predicted value) or uncontrolled asthma [1] and to have a post-bronchodilator FEV_1 >60% of predicted value in order to be eligible for randomization. Exclusion criteria were defined as any of the following: current or ex-smokers (>10 pack-years); pregnant or lactating; severe asthma exacerbation during the run-in period; 3 or more courses of oral corticosteroids in the previous 6 months; hospitalization due to asthma in the previous 6 months; any course of oral corticosteroids 30 days prior to screening; concomitant lung disease; treatment with anti-cholinergics, antihistamines, leukotriene receptor antagonists, beta blockers, tricyclic antidepressant, methylxantines, ritonavir, or ketoconazole in the previous 2 weeks; or a morning cortisol level lower than 5 mcg/dL.

Protocol outcome measures

The primary end point for the determination of efficacy of study treatments was the mean change in morning PEF. Patients used diaries in order to document morning and evening PEF, document answers to questions of the Asthma Control Questionnaire (ACQ-7 validated in Brazil and allowed for use in this study) [23,24], and to keep record of salbutamol and other medication use. Diaries were collected at each study visit. Patients performed a measured morning and evening PEF by using a portable PIKO-1 peak flow meter (nSpire Health Inc). All measurements were documented in diaries and the highest of the 3 results was automatically recorded in a calendar. The patients underwent spirometry (in accordance with the Brazilian Thoracic Society [25]) at screening and at each of the study visits. Reference ranges were calculated based on statistics formulated from the Brazilian population [26,27]. Patients recorded their use of rescue medication as the number of puffs of salbutamol taken in each 24-h period. At week 12, investigators rated each patient's response to therapy compared with their baseline in a 5-point scale from 1 (much improved) to 5 (much worse). Medication use was measured by the assessment of used blister packs (for FL/F) and by a dose counter (for BD/F).

Daily data collection included the morning and evening PEF and asthma control days. For PEF analysis, however, it was used the average of 2 weeks run in period and 2 weeks period before follow-up visits. To the asthma control analysis, it was also measured the average of the Asthma Control Questionnaire score during the 2-week baseline and at 2 weeks before follow-up visits.

Safety assessments

Adverse events were reported throughout the study period. A physical examination (including an oropharyngeal examination and vital signs measurements) was performed at the pre-randomization visit and at each subsequent visit (day 1, weeks 4, 8, and 12). Clinical laboratorial tests (complete blood count, serum glucose, serum potassium, plasma cortisol, and a 24-h urinary free cortisol) and a 12−lead ECG were performed at baseline and at the end of the study.

Statistics

A sample size of 180 patients and a standard deviation (SD) of 45 L/min were required in order to provide a power of 80% with respect to non-inferiority. Non-inferiority was concluded if the lower limit of the 97.5% confidence interval (CI) for the treatment difference (fluticasone/formoterol − budesonide/formoterol) was ≥−20 L/min.

Efficacy and safety were based on the intention-to-treat (ITT) population, defined as patients who had taken at least 1 dose of the study medication and provided some post-baseline efficacy data. A per-protocol population (PP) analysis was also included e reported. The reasons for early discontinuation included lack of compliance, patient request, adverse effects, or pre-defined reasons for discontinuation.

The Student's *t* test was used for comparing baseline variables between the groups, absolute means related to lung function, asthma control scores, and measurements of rescue medication. The number of patients with asthma exacerbations was analyzed using Chi-square test. Changes in lung function from baseline were measured *via* analysis of covariance with the fixed effect of treatment and the baseline as a covariate. Changes in laboratory analysis from baseline were compared using the Student's *t* test (parametric) or Mann–Whitney test (non-parametric) according to the statistical distribution.

Descriptive statistics included: counts and percentages for categorical variables; means and standard deviations for normally distribution variables; and medians, including variables defined by first and third quartiles, that were not normally distributed on the original or log-transformed scales (SAS® statistical-analysis software, version 9.1.3, was used for these analyses).

Results

Overall, 274 patients were enrolled and 196 patients were randomized and entered the treatment period (97 patients were randomly assigned to the FL/F arm and 99 to the BD/F arm). Patient flow and baseline characteristics are shown in Fig. 1 and Table 1. In the fluticasone/formoterol and budesonide/formoterol groups, 84 and 85 patients completed the study and were included in the per-protocol (PP) analysis, respectively. The treatment groups of the ITT population were comparable in terms of their demographical and baseline characteristics (Table 1).

Table 1 Baseline characteristics of the 196 patients.

	FL/F	BD/F	*p* Value
Female sex — no. (%)	74 (76.3)	72 (72.7)	0.56
Age — years	34.5 ± 15.0	35.6 ± 17.6	0.65
Caucasian race — no. (%)	65 (67.0)	71 (71.7)	0.33
Duration of asthma — years	22.8 ± 13.2	21.4 ± 13.4	0.40
Weight — kg	68.2 ± 14.8	65.9 ± 15.2	0.28
Ex-smoker — no. (%)	14 (14.4)	10 (10.1)	0.35
Morning PEF — L/min	355.6 ± 115.5	345.1 ± 124.2	0.54
Evening PEF — L/min	362.5 ± 121	351.4 ± 123.5	0.53
FEV_1 — L	2.51 ± 0.71	2.50 ± 0.77	0.95
FEV_1% — % predicted	85.5 ± 18.6	85.2 ± 17.6	0.90
ACQ-7 score[a]	0.93 ± 0.69	0.87 ± 0.64	0.52

FL/F: Fluticasone propionate/formoterol group; BD/F: Budesonide/formoterol group; PEF: Peak expiratory flow; FEV_1: forced expiratory volume in 1 s; ACQ: Asthma Control Questionnaire.
Data expressed as mean ± SD.
[a] Scores on the Asthma Control Questionnaire range from 0 to 6, with a higher score indicating worse asthma control; the minimal important difference (MID) is 0.5.

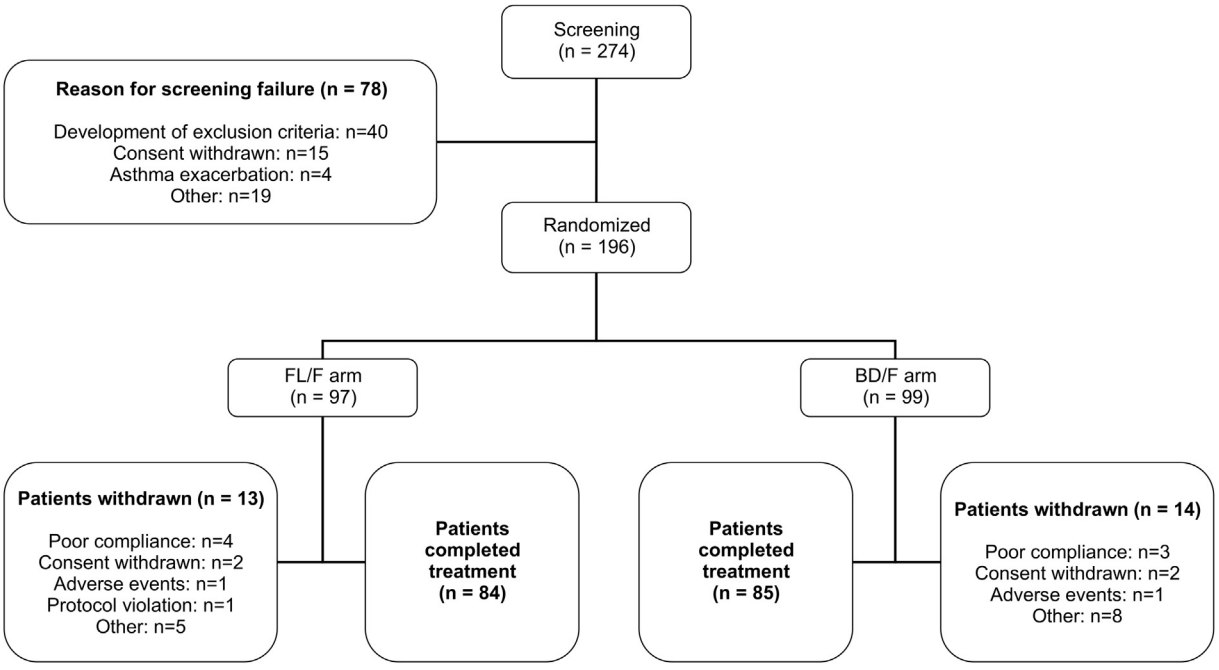

Figure 1 Flow of patients. BD/F: budesonide/formoterol; FL/F: Fluticasone propionate/formoterol.

The majority of patients were Caucasian (69.4%) and female (74.5%). The average age was 35.1 years, with 19.9% adolescents aged between 12 and 18 years. The mean baseline FEV_1 before bronchodilation was 2.50 ± 0.74 L (85.3 ± 18% of the predicted value). There were no differences in terms of demographical and baseline characteristics in the treatment groups of the PP population.

Patient compliance was greater in the FL/F group than the BD/F group (mean percentage of administered drug 93.8 ± 9.9% in FL/F versus 87.2 ± 12.9 in BD/F).

Primary outcome

For both treatment groups, average morning PEF was automatically recorded by peak flow meter and increased significantly by week 12 (both $p < 0.05$) (Fig. 2). Non-inferiority was achieved in the ITT and PP analysis with respect to morning PEF as the lower limit of the CI for the treatment differences (−12.6 L/min in the ITT population) was > of 20 L/min for the morning PEF, as recorded using peak flow meter. There was no significant difference in the change from baseline between treatment groups (Table 2) (Fig. 3).

Secondary outcomes

The mean FEV_1 values for the FL/F group at baseline, week 4, week 8, and week 12 were 2.52 L, 2.66 L, 2.71 L, and 2.67 L, respectively. For the BD/F group the mean FEV_1 values at baseline, week 4, week 8, and week 12 were 2.51 L, 2.50 L, 2.49 L, and 2.53 L, respectively. An increase from the baseline FEV_1 was observed in the FL/F treatment group at weeks 4, 8, and 12 and were statistically significant (all with $p < 0.01$). There was no statistically significant change from the baseline during any period of evaluation in the BD/F group. In addition, the increase in the mean FEV_1 from baseline to week 12 was significantly greater in patients receiving FL/F than in patients receiving BUD/F (Table 2). The time course of change in FEV_1 for the PP population is shown at Fig. 2.

We observed in both groups a statistically significant improvement in the ACQ7 score from baseline (mean values at baseline and at the end of the study were 0.93 to 0.64 in the FL/F group, respectively; and 0.87 to 0.73 in the BD/F group, respectively; $p < 0.01$ for both groups). In the FL/F group, A statistically significant difference was observed in the ACQ7 score from baseline to week 12 ($p = 0.02$) (Table 2). With regards to rescue salbutamol use, the FL/F group showed less use over the time of the study (mean values at baseline and at the end of the study were, 1.1 and 0.57 puffs/day, respectively; $p < 0.01$). The BD/F group failed to show a statistically significant reduction in rescue salbutamol use (mean values at baseline and at the end of the study were 0.71 and 0.60 puffs/day, respectively; $p = 0.058$). There were no statistically significant differences from baseline to the end of the study in terms of the evening PEF.

In the ITT population, there were no statistically significant differences between treatment groups when considering either the change in the evening PEF or the use of rescue salbutamol from baseline to week 12 ($p = 0.19$, $p = 0.29$; respectively) (Table 2).

For all secondary outcomes, PP analysis showed similar results.

At week 12, 78.6% of the patients in the FL/F group and 69.4% of the patients in the BD/F group were rated by investigators as "improved" or "much improved"; this

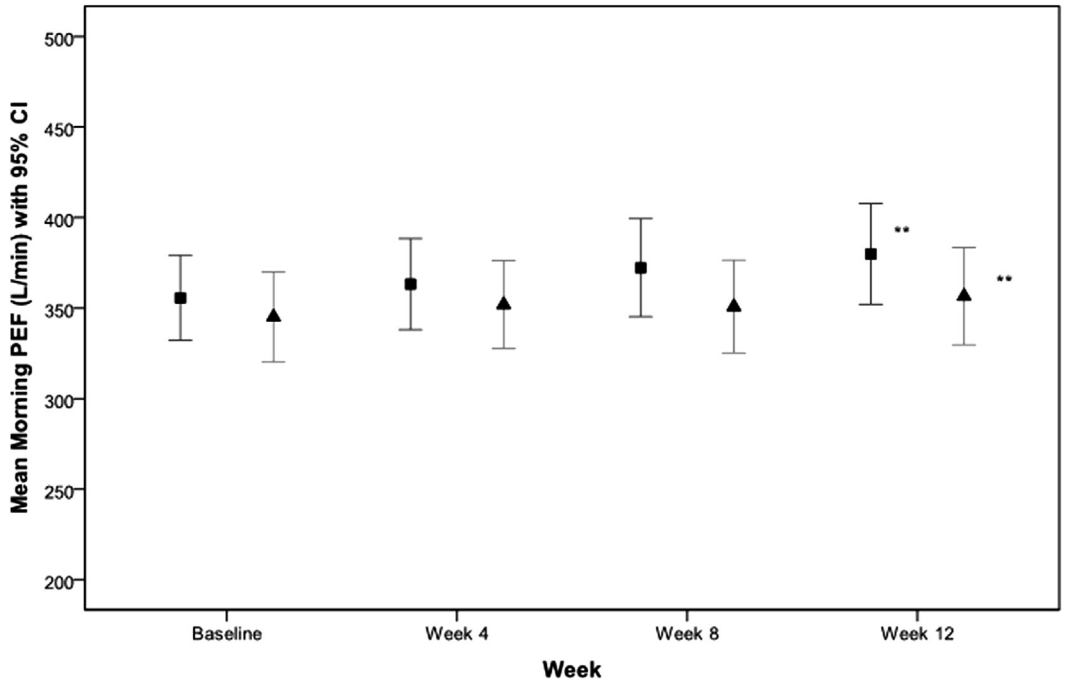

Figure 2 Change over time of the morning PEF in the intention to treat population. ■: Fluticasone/formoterol; ▲: Budesonide/formoterol; **$p < 0.05$ versus baseline using last observation carried forward procedure.

Table 2 Outcome variables in the intention-to-treat population (mean change from baseline).

	FL/F	BD/F	*p* Value
Morning PEF − L/min			
Baseline (Mean ± SD)	355.6 (115.5)	345.1 (124.2)	
End of Study (Mean ± SD)	379.9 (137.3)	356.6 (134.4)	
Change from baseline (Mean ± SD)	24.3 (85.9)	11.5 (92.6)	0.32
Evening PEF − L/min			
Baseline (Mean ± SD)	362.5 (121.0)	351.4 (123.5)	
End of Study (Mean ± SD)	380.5 (129.7)	355.3 (131.0)	
Change from baseline (Mean ± SD)	18.0 (78.1)	3.9 (73.9)	0.19
Prebroncodilatador FEV_1 − L			
Baseline (Mean ± SD)	2.52 (0.71)	2.51 (0.77)	
End of Study (Mean ± SD)	2.66 (0.74)	2.52 (0.73)	
Change from baseline (Mean ± SD)	0.14 (0.41)	0.01 (0.27)	0.01
FEV_1 − percent of predicted value before bronchodilation			
Baseline (Mean ± SD)	85.8 (18.8)	85.3 (17.4)	
End of Study (Mean ± SD)	91.2 (19.4)	86.2 (16.6)	
Change from baseline (Mean ± SD)	5.4 (11.1)	0.9 (10.5)	<0.01
Salbutamol rescue use − puffs/day			
Baseline (Mean ± SD)	1.10 (2.57)	0.71 (1.09)	
End of Study (Mean ± SD)	0.57 (1.25)	0.61 (1.17)	
Change from baseline (Mean ± SD)	−0.53 (2.46)	−0.08 (0.75)	0.29
ACQ7 score			
Baseline (Mean ± SD)	0.93 (0.69)	0.87 (0.64)	
End of study (Mean ± SD)	0.64 (0.63)	0.73 (0.65)	
Change from baseline (Mean ± SD)	−0.30 (0.48)	−0.14 (0.47)	0.02

Data are presented as mean ± SD. FL/F: Fluticasone propionate/formoterol group; BD/F: Budesonide/formoterol group; PEF: peak expiratory flow; FEV_1: forced expiratory volume in 1 s; ACQ: Asthma Control Questionnaire.

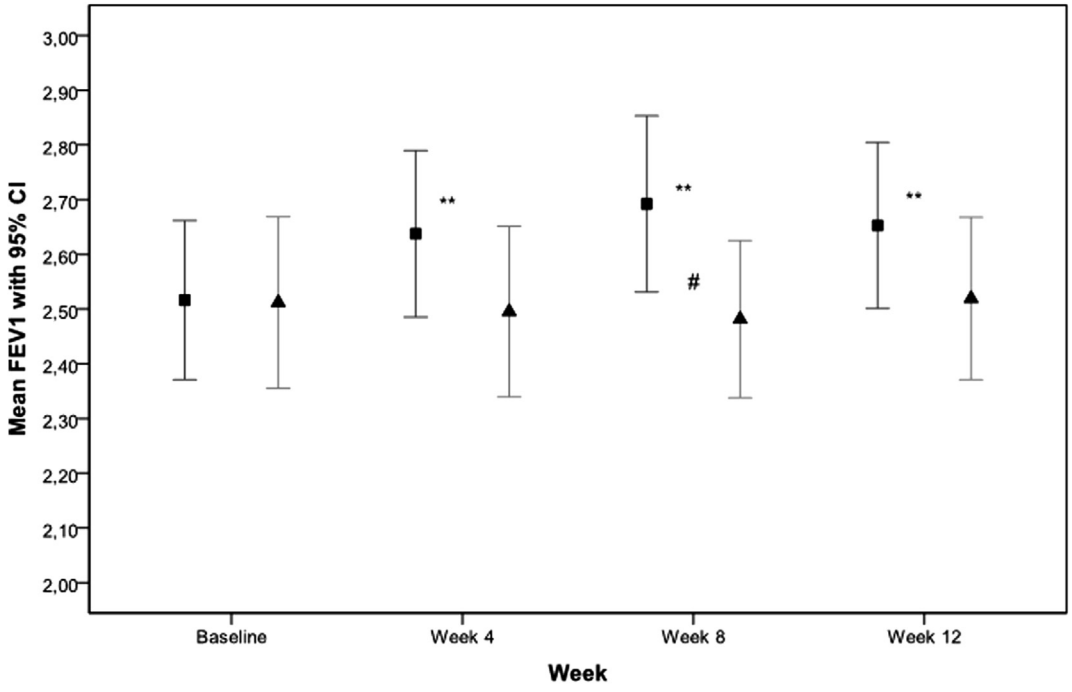

Figure 3 Change over time in FEV_1 in the intention to treat population. ■: Fluticasone/formoterol; ▲: Budesonide/formoterol; $^{**}p < 0.05$ versus baseline using last observation carried forward (LOCF) procedure; $^{\#}p < 0.05$ between treatments using LOCF procedure.

difference between the groups was not statistically significant ($p = 0.29$).

Tolerability

During the study, 193 non-serious adverse events were reported: 93 among patients receiving fluticasone/formoterol and 100 among patients receiving budesonide/formoterol. The most commonly reported adverse events are listed in Table 3. Oral candidiasis was infrequent, occurring only in 1 patient receiving budesonide/formoterol. A total of 5 serious adverse events occurred: 2 among patients receiving fluticasone/formoterol (1 patient who underwent elective, gynecologic surgery and 1 patient who experienced a post-procedural headache) and 3 among patients receiving budesonide/formoterol (1 patient who developed pneumonia, 1 patient who developed facial nerve palsy, and 1 patient who was found to have a gallstone). Six patients in each group experienced a severe asthma exacerbation requiring an oral corticosteroid and 1 patient in each treatment group discontinued the study because of adverse events.

Laboratory evaluations showed no statistically significant differences between the treatment groups. A small increase in aspartate aminotransferase and in alanine aminotransferase (mean 7.7 U/L and 3.8 U/L, respectively) was observed in the FL/F group; however, this was not considered to be clinically significant. There were no differences between treatment groups in terms of the change from baseline with regards to the $8{:}00_{AM}$ serum cortisol concentration ($p = 0.10$) or the 24-h urinary free cortisol ($p = 0.36$). Blood pressure and heart rate were stable throughout the study period in both treatment groups with no clinically relevant changes.

Discussion

This is the first study to evaluate and compare the combination of fluticasone propionate plus formoterol administered *via* a dry powder inhaler to budesonide plus formoterol in uncontrolled asthma patients. The results of the study show the non-inferiority of fluticasone propionate plus formoterol to budesonide plus formoterol during 12-weeks on the basis of the predefined criteria of morning PEF. Morning PEF, rescue medication use, and asthma control improved in relation to the baseline in both treatment groups. A greater improvement in FEV_1 and asthma control was also seen in uncontrolled and partly controlled asthma patients who used FL/F compared to those who used BD/F, with no difference considering need to rescue therapy and PEF measures.

The observed improvement in the pre-bronchodilator FEV_1 and asthma control with the fixed combination FL/F may be related to the efficacy of the fluticasone propionate component. Experimental studies have shown that fluticasone propionate shows a higher affinity for the human glucocorticoid receptor [28] than does budesonide and has superior *trans*-repress AP-1 or NF-kB activity [4]. Clinical experience has also shown an increase in lung function after treatment with fluticasone propionate relative to budesonide, as demonstrated by improvements in morning PEF observed in a meta-analysis involving 7 comparative trials [29].

The difference in efficacy observed may be also related to the type of inhaler. Both medications were administrated *via* a dry powder inhaler. However, therapy compliance [30] and delivery of the drug to the lungs [31] may change with the use of different DPI, and FL/F was administrated using an inhaler with improvements to reduce patients with difficult to handle the inhaler (easier to open the lid and to pierce the capsule, more friendly designed) [32]. In our study, we observed better compliance with the FL/F inhaler which may have contributed to the better results of combining fluticasone and formoterol.

The clinical relevance of these statistical differences is difficult to estimate. Pre-bronchodilator FEV_1 is a strong, independent predictor of the risk of asthma exacerbations [29]. However, based on studies of the subjective perception by patients, the minimal increase required in FEV_1 for a patient to notice improvement is about 0.23 L (or 10%) [33,34]. Based on this data, the difference observed in our study may not be clinically significant. Likewise, a change of 0.5 in the ACQ has been reported as the cut off for clinical improvement [34]. Therefore, the difference in the ACQ observed in our study may not be clinically significant, either.

During the 3-month study period, the FL/F combination was tolerated just as well as the BUD/F combination. The most common adverse effects in each group (influenza-like symptoms and asthma exacerbations) can probably be attributed to seasonal factors, as suggested by their similar frequency in the 2 groups. There was no evidence of detrimental effects on the cardiovascular system (no changes in ECG tracings) or the adrenal axis (based on morning cortisol levels and 24-h urinary free cortisol levels).

A limitation of the present study is the open label design. However, the results are unlikely to be influenced by investigator bias, by design, or by converting all patients to BUD/F during run-in. It could be argued that these may have encouraged patients to be more motivated in FL/F arm, leading to an inbuilt bias influencing patient's behavior and adherence. However, a number of precautions were taken to minimize bias. First, expectation bias was minimized by training all patients to use correctly the inhalation device and by stressing the relevance of the correct use of treatment and compliance at each visit. Second, to reduce expectation bias of patients and investigators [35] we chose as primary outcome an objective measure. It is impossible to determine whether how

Table 3 Adverse events occurring in >2% of patients in either treatment group in the intention-to-treat population.

Adverse event	FL/F	BD/F
Influenza-like symptoms	8 (8.2)	13 (13.2)
Asthma exacerbation	10 (10.3)	12 (12.1)
Headache	11 (11.3)	4 (4)
Upper respiratory tract infection	8 (8.2)	4 (4.0)
Sinusitis	4 (4.1)	3 (3.0)
Cough	1 (1.0)	3 (3.0)

Data are presented as number (%). FL/F: Fluticasone propionate/formoterol group; BD/F: Budesonide/formoterol group.

switching to a new inhalation device influenced the study results because it may affect adherence in two opposite ways: increasing adherence due to motivation/hope or reducing adherence due to the individual preferences [36]. Finally, we also performed a PP analysis without non-adherent patients and the results were the same.

As a consequence of our study design, we cannot comment on either the rate of asthma exacerbation or long-term safety issues. Longer longitudinal studies, with sufficient statistical power, will be needed in order to evaluate exacerbations and additional safety events.

In conclusion, this study showed the non-inferiority of the combination of FL/F to BD/F in asthmatics not controlled with other ICS/LABA combinations. The data also suggests an improvement in terms of lung function and asthma control after 12-weeks of treatment in patients using the combination FL/F. The findings of this study support the use of fluticasone propionate plus formoterol (as a dry powder combination) as an option in treating uncontrolled asthma patients. Many asthmatic patients still show poor control despite of the use of combination therapy. As an alternative for asthma treatment, this formulation may offer a new option in asthma medication and delivery when considering patient preference and treatment response. Further double blind studies powered to evaluated superiority are required to establish differences between therapies.

References

[1] GINA. Global Initiative for Asthma. Date last updated. Date last accessed: January 2013. Available from:, http://www.ginasthma.com; December 2012.

[2] Murphy KR, Bender BG. Treatment of moderate to severe asthma: patient perspectives on combination inhaler therapy and implications for adherence. J Asthma Allergy 2009;2:63—72.

[3] Howell G. Nonadherence to medical therapy in asthma: risk factors, barriers, and strategies for improving. J Asthma 2008;45:723—9.

[4] Jaffuel D, Demoly P, Gougat C, Balaguer P, Mautino G, Godard P, et al. Transcriptional potencies of inhaled glucocorticoids. Am J Respir Crit Care Med 2000;162:57—63.

[5] Esmailpour N, Högger P, Rabe KF, Heitmann U, Nakashima M, Rohdewald P. Distribution of inhaled fluticasone propionate between human lung tissue and serum in vivo. Eur Respir J 1997;10:1496—9.

[6] Luijk B, Kempsford RD, Wright AM, Zanen P, Lammers JWJ. Duration of effect of single-dose inhaled fluticasone propionate on AMP-induced bronchoconstriction. Eur Respir J 2004;23:559—64.

[7] Adams NP, Bestall JC, Lasserson TJ, Jones P, Cates CJ. Fluticasone versus placebo for chronic asthma in adults and children. Cochrane Database Syst Rev 2008. CD003135.

[8] Palmqvist M, Persson G, Lazer L, Rosenborg J, Larsson P, Lötvall J. Inhaled dry-powder formoterol and salmeterol in asthmatic patients: onset of action, duration of effect and potency. Eur Respir J 1997;10:2484—9.

[9] O'Byrne PM, Bisgaard H, Godard PP, Pistolesi M, Palmqvist M, Zhu Y, et al. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. Am J Respir Crit Care Med 2005;171:129—36.

[10] Bodzenta-Lukaszyk A, Pulka G, Dymek A, Bumbacea D, McIver T, Schwab B, et al. Efficacy and safety of fluticasone and formoterol in a single pressurized metered dose inhaler. Respir Med 2011;105:674—82.

[11] Bodzenta-Lukaszyk A, Dymek A, McAulay K, Mansikka H. Fluticasone/formoterol combination therapy is as effective as fluticasone/salmeterol in the treatment of asthma, but has a more rapid onset of action: an open-label, randomized study. BMC Pulm Med 2011;11:28.

[12] Bodzenta-Lukaszyk A, Buhl R, Balint B, Lomax M, Spooner K, Dissanayake S. Fluticasone/formoterol combination therapy versus budesonide/formoterol for the treatment of asthma: a randomized, controlled, non-inferiority trial of efficacy and safety. J Asthma 2012;49:1060—70.

[13] Nathan RA, D'Urzo A, Blazhko V, Kaiser K. Safety and efficacy of fluticasone/formoterol combination therapy in adolescent and adult patients with mild-to-moderate asthma: a randomised controlled trial. BMC Pulm Med 2012;12:67.

[14] Dissanayake S, Grothe B, Kaiser K. Fluticasone/formoterol: a new single-aerosol combination therapy for patients with asthma. Respir Med 2012;106(Suppl.):S20—8.

[15] Corren J, Mansfield LE, Pertseva T, Blahzko V, Kaiser K. Efficacy and safety of fluticasone/formoterol combination therapy in patients with moderate-to-severe asthma. Respir Med 2013;107:180—95.

[16] McKeage K. Fluticasone propionate/formoterol fumarate: a review of its use in persistent asthma. Drugs 2013;73:195—206.

[17] Bodzenta-Lukaszyk A, Van Noord J, Schröder-Babo W, McAulay K, McIver T. Efficacy and safety profile of fluticasone/formoterol combination therapy compared to its individual components administered concurrently in asthma: a randomised controlled trial. Curr Med Res Opin 2013;29:579—88.

[18] Neffen H, Fritscher C, Schacht FC, Levy G, Chiarella P, Soriano JB, et al. Asthma control in Latin America: the asthma insights and reality in Latin America (AIRLA) survey. Rev Panam Salud Publica 2005;17:191—7.

[19] Ponte EV, Petroni J, Ramos DCB, Pimentel L, Freitas DN, Cruz AA. Perception of asthma control in asthma patients. J Bras Pneumol 2007;33:635—40.

[20] FitzGerald JM, Boulet L-P, McIvor RA, Zimmerman S, Chapman KR. Asthma control in Canada remains suboptimal: the Reality of Asthma Control (TRAC) study. Can Respir J 2006;13:253—9.

[21] Gamble J, Stevenson M, Heaney LG. A study of a multi-level intervention to improve non-adherence in difficult to control asthma. Respir Med 2011;105:1308—15.

[22] Horne R. Compliance, adherence, and concordance: implications for asthma treatment. Chest 2006;130:65S—72S.

[23] Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. Eur Respir J 1999;14:902—7.

[24] Leite M, Ponte EV, Petroni J, D'Oliveira Júnior A, Pizzichini E, Cruz AA. Evaluation of the asthma control questionnaire validated for use in Brazil. J Bras Pneumol 2008;34:756—63.

[25] Pereira CAC, Jansen JM, Menna Barreto SS, Martinho J, Sulmonett NDR. Espirometria. J Pneumol 2002;28:1—82.

[26] Pereira CA de C, Sato T, Rodrigues SC. New reference values for forced spirometry in white adults in Brazil. J Bras Pneumol 2007;33:397—406.

[27] Ladosky W, Andrade RT, Loureiro NG, Botelho MAM. Comparação entre os valores teóricos para alguns dados espirométricos em crianças determinados pelas equações de Mallozi e de Polgar. J Pneumol 2002;28:125—30.

[28] Esmailpour N, Högger P, Rohdewald P. Binding kinetics of budesonide to the human glucocorticoid receptor. Eur J Pharm Sci 1998;6:219—23.

[29] Barnes NC, Hallett C, Harris TA. Clinical experience with fluticasone propionate in asthma: a meta-analysis of efficacy and systemic activity compared with budesonide and

beclomethasone dipropionate at half the microgram dose or less. Respir Med 1998;92:95—104.
[30] Voshaar T, Kostev K, Rex J, Schröder-Bernhardi D, Maus J, Munzel U. A retrospective database analysis on persistence with inhaled corticosteroid therapy: comparison of two dry powder inhalers during asthma treatment in Germany. Int J Clin Pharmacol Ther 2012; 50:257—64.
[31] O'Byrne PM. Clinical comparisons of inhaler systems: what are the important aspects? J Aerosol Med 1995;8(Suppl. 3):S39—46 [discussion S47].
[32] Pereira LFF, Toufen Jr C. Impact that display an educational film, changes in powder inhaler device and in the instructions given to the patient have on the inhaler handling skill. RBM 2011;68:22—7.
[33] Santanello NC, Zhang J, Seidenberg B, Reiss TF, Barber BL. What are minimal important changes for asthma measures in a clinical trial? Eur Respir J 1999;14:23—7.
[34] Reddel HK, Taylor DR, Bateman ED, Boulet L-P, Boushey HA, Busse WW, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. Am J Respir Crit Care Med 2009; 180:59—99.
[35] Gluud LL. Bias in clinical intervention research. Am J Epidemiol 2006;163:493—501.
[36] Lavorini F, Magnan A, Dubus JC, Voshaar T, Corbetta L, Broeders M, et al. Effect of incorrect use of dry powder inhalers on management of patients with asthma and COPD. Respir Med 2008;102:593—604.